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Synopsis

Paramedic analgesia comparing ketamine and morphine in trauma. A synopsis of the PACKMaN double-blind RCT

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Abstract

Background: Paramedics frequently administer analgesic medications for pain following trauma. Morphine is the most commonly administered strong analgesic. However, it may not be the best option as it may lower blood pressure, depress respiration and there is a risk of dependency. Ketamine might be a better option. We sought to compare clinical and cost-effectiveness of paramedic administered ketamine and morphine in patients with severe pain following trauma.

Methods: PACKMaN was a double-blinded, randomised controlled, superiority trial. Eligible patients were 16 years of age or over, had an acute injury, and articulated a pain score of 7 or greater on a 0–10 numeric rating score. We excluded pregnant patients, prisoners, those unable to articulate a pain score and anyone lacking capacity. The maximum dose of morphine was 20 mg while the maximum dose of ketamine was 30 mg. The trial drug was titrated to effect. The primary outcome was the Sum of Pain Intensity Difference score.

Results: We randomised 449 participants: 219 (49%) received ketamine and 230 (51%) received morphine. The Sum of Pain Intensity Difference score was 3.5 (standard deviation 2.8) for ketamine and 3.4 (standard deviation 3.0) for morphine. We found no significant difference in efficacy between drugs (adjusted mean difference 0.1, 95% confidence interval −0.4 to 0.6; $p = 0.7$). Ketamine was more likely to achieve 'very much improvement' (odds ratio 1.58, 95% confidence interval 1.08 to 2.31; $p = 0.019$) and to do so more rapidly than morphine (hazard ratio 1.42, 95% confidence interval 1.09 to 1.84; $p = 0.009$). However, morphine was likely to last longer than ketamine (hazard ratio 1.28, 95% confidence interval 1.05 to 1.56; $p = 0.013$). There was no evidence of a significant difference in serious adverse events.

Conclusion: Ketamine does not provide superior analgesia than morphine when treating acute severe trauma pain. Ketamine is a suitable alternative that is safe for use by paramedics.

Limitations: Patients were required to provide verbal assent to participate, consequently we were only able to recruit patients who had capacity to understand what was being asked of them. It is also therefore probable that we were unable to recruit the most severely injured patients. These factors may limit generalisability of our results. Furthermore, we were unable to complete a planned sensitivity analysis to determine if there was a difference in treatment response between patients with more minor injuries and those who were more severely injured.

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Finally, we experienced a loss to follow-up at 3 and 6 months, so our findings for long term outcomes may have been underpowered.
Future work: Future research should focus on identification of the optimal drug (or combination of drugs), dosing and drug route to achieve rapid control of pain. In addition, it would be valuable to explore the relationship between paramedic analgesia and the development of chronic pain.
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Introduction

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The International Association for the Study of Pain (IASP) define pain as 'an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage'.[2] Pain may further be described according to its anatomic location (e.g. chest or limb pain), time course (e.g. acute or chronic) or in relation to underlying pathology (e.g. trauma or cancer related).[3] The IASP definition of pain acknowledges that pain incorporates both emotional and sensory components arguing that it is not simply a sensation.[4] The Declaration of Montreal asserts that effective pain management should be a basic human right.[5] This led the World Health Assembly to subsequently declare that 'it is the ethical duty of every healthcare professional to alleviate pain and suffering'.[6] Pain management is therefore a key priority for ambulance clinicians.[7]

Acute pain following trauma is a common presenting complaint for ambulance clinicians. It has been reported that up to 24% of ambulance calls are related to trauma.[8] Published data indicate that pain is present in at least 70% of trauma patients attended by ambulance services.[9] Furthermore, where a pain score is documented, 81% of patients report moderate or severe pain.[9]

There are several adverse physiologic effects associated with poorly managed acute severe pain. Pain triggers several complex haemodynamic, respiratory, metabolic, neurohumoral, immune and somatosensory responses.[10] It is widely recognised that pain can precipitate an increase in both heart rate and blood pressure.[11] Tachycardia raises myocardial metabolic demand and increases risk of arrhythmia.[12] In the context of acute trauma where there is potential for blood loss, elevated blood pressure may increase the risk of clot disruption and exacerbate blood loss.[13] Furthermore, thoracic musculoskeletal pain is known to impede chest expansion leading to shallow breathing with subsequent increased dead space ventilation.[14] This can result in impaired gas exchange, increasing the risk of respiratory failure.[14] Finally, pain can trigger increased levels of cortisol, catecholamines and glucagon as well as decreased insulin sensitivity.[15]

Unfortunately, evidence suggests that acute pain is poorly managed within ambulance services.[7,16–19] There are several potential explanations for this finding. The prehospital interval is short and there may be insufficient time for drugs to reach their therapeutic effect. Training of paramedics may be inadequate, altered patient physiology and a limited formulary may all contribute to suboptimal prehospital pain management.

Irrespective of the underlying cause, poorly managed acute pain is associated with adverse patient outcomes,[20] including depression,[21] post-traumatic stress disorder[22] and chronic pain.[23] Chronic pain is defined as pain that persists, or recurs, for more than 3 months,[24] and it is associated with significant economic and social burden.[25–27] Conservative estimates of pain-related healthcare costs suggest a global burden of $560–635 billion annually.[26] In the UK, the economic consequence of chronic pain has been estimated at £8000 per person, per year.[27]

A direct relationship has been established between acute pain severity and chronic pain.[23] The transition from acute to chronic pain appears to occur in discrete pathophysiological and histopathological steps.[28] Persistent pain activates secondary mechanisms, peripherally and centrally, leading to allodynia, hyperalgesia and hyperpathia that impair normal functioning. These changes sensitise second-order spinal neurones which facilitates the transition of acute to chronic pain.[28] However, evidence suggests

that effective treatment of acute pain can reduces the risk of developing chronic pain.[28,29]

Several pharmacologic options exist to treat acute pain. The World Health Organization (WHO) categorise analgesic drugs as non-opioids such as nonsteroidal anti-inflammatory drugs, moderate opioids such as codeine, strong opioids such as morphine and analgesic adjuvants.[30] Analgesic adjuvants are drugs typically indicated for conditions other than pain but may be effective in some pain conditions; for example, steroids modulate the inflammatory response, they reduce swelling and in doing so dampen the pain stimulus.[31] The WHO further advocate the use of a 'pain ladder', starting therapy on the first step with non-opioids for mild pain, the second step with moderate opioids for moderate pain, and the third step with opioids for severe pain. If analgesia is not achieved at lower levels then clinicians are encouraged to escalate to the next step to achieve adequate analgesic effect.[30]

Each of the three steps of the WHO analgesic ladder is reflected within the ambulance service pain management guidelines.[32] At the first step, paramedics may administer paracetamol or ibuprofen. At the intermediate step, paramedics can administer oral morphine and at the top step they can administer parenteral morphine. Paramedics also have the option of Entonox and, in some services, methoxyflurane. Both are short acting, inhalation analgesics that can be used for moderate or severe pain. Existing ambulance guidelines encourage ambulance paramedics to offer patients inhalation analgesia while they wait for enteral or parenteral analgesia to take effect.[32] Paramedics are additionally able to administer anti-emetic drugs, including metoclopramide and ondansetron, for vomiting that may act as an adjuvant when analgesia is administered orally.

Several additional treatment options exist for the management of acute severe pain. Historically, morphine and fentanyl have been the preferred options in the emergency setting.[33] However, in some parts of the world, there is rising concern relating to prescription of opioid drugs and opioid use disorder.[34] In addition, fentanyl is not currently accessible for paramedics due to restrictions imposed by medicines legislation. Alternatives to opioid therapy include ketamine[35] and, in selected cases, regional nerve blocks.[36] There are an increasing number of trials reporting the efficacy of sub-dissociative ketamine to provide analgesia in the emergency department.[37–40] There is also growing use of, ketamine by prehospital critical care teams; however, robust evidence of its effectiveness in the prehospital setting when used by non-specialist paramedics is currently lacking.

Summary of existing evidence

We identified 6 randomised controlled trials (RCTs),[41–46] 22 observational studies[47–69] and 4 systematic reviews[70–73] reporting effectiveness of prehospital ketamine. Information bias was a key limitation of all identified studies due to their unblinded methodology and the subjective nature of pain scoring.[74]

Ketamine versus placebo

One RCT (n = 40) compared 0.75 mg/kg intranasal ketamine versus placebo (saline) when administered by paramedics.[41] This study reported that pain scores [documented with visual analogue scale (VAS) pain score] reduced by 80% in the ketamine group versus 60% in the placebo group at 30 minutes.[41] No serious adverse effects were reported.

Ketamine versus morphine

Two randomised trials (n = 563) compared ketamine and morphine.[42,43] Both studies were unblinded, non-inferiority trials among physicians. Tran *et al.*[42] conducted a cluster randomised trial in rural Vietnam. Trauma patients (n = 312) received either intravenous (IV) ketamine (0.2–0.3 mg/kg) or intramuscular morphine (10 mg in adults, 5 mg in children). The rural nature of the trial meant that most patients were transported to the physician, rather than the physician attending the scene. Hence, the prehospital interval was significant – mean time from injury to hospital admission was 3.6 hours [95% confidence interval (CI) 3.3 to 4.0 hours]. Pain intensity was measured using a VAS. The final reduction in VAS pain intensity was −3.5 in the ketamine group versus −3.1 in the morphine group. The side-effect profile was superior for ketamine with less vomiting observed than for morphine (19% difference, 95% CI 8% to 22%), although there was a higher rate of hallucinations and agitation (1.5% difference) in patients receiving ketamine. The authors concluded that ketamine yielded an analgesic effect equal to that provided by morphine.[42]

Le Cornec *et al.*[43] similarly conducted a trial among physicians in France. Trauma patients (n = 251) with moderate or severe pain [numeric rating score (NRS) > 4] were randomised to either 2–3 mg (dependent upon weight) of IV morphine every 5 minutes or 20 mg of IV ketamine over 2 minutes followed by a further 10 mg every 5 minutes. The final reduction in NRS pain intensity was −3.7 (95% CI −4.2 to −3.2) in the ketamine group versus −3.8 (95% CI −4.2 to −3.4) in the morphine group (difference 0.1, 95% CI −0.7 to 0.9). The authors similarly concluded that ketamine was not inferior to morphine and a suitable alternative for patients with acute traumatic pain.

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Ketamine combined with morphine versus morphine alone

Three randomised trials (*n* = 235) compared a combination of ketamine and morphine versus morphine alone.[44–46] In one trial (*n* = 135), paramedics administered 5 mg IV morphine to all patients and thereafter randomised patients to receive either ketamine or morphine.[44] The mean pain score change was 5.6 (95% CI 6.2 to 5.0) in the morphine and ketamine group compared to 3.2 (95% CI 3.7 to 2.7) in the morphine-only group. Ketamine and morphine was associated with a higher incidence of side effects than morphine alone (risk difference 26.3%, 95% CI 10.6% to 40.7%).

In the second trial (*n* = 27) paramedics administered either 0.1 mg/kg morphine sulphate combined with 0.2 mg/kg ketamine or 0.2 mg/kg of morphine sulphate alone.[45] Reported pain scores were lower for the ketamine and morphine group (3.1 ± 1.4) than for the morphine-only group (5.4 ± 1.9).

In the third trial (*n* = 73) physicians administered 0.1 mg/kg IV morphine to all patients and thereafter randomised patients to receive either 0.2 mg/kg of ketamine and 3 mg of morphine every 5 minutes as required or to administer 3 mg of morphine with a placebo every 5 minutes as required.[46] The primary outcome was change in VAS pain score at 30 minutes. There was no significant difference in change in pain score at 30 minutes ketamine and morphine 34.1 (25.6–42.6), morphine and placebo 39.5 (32.4–46.6).[46] The authors further reported no difference in side effects between drug combinations.

No trials compared morphine alone versus ketamine alone versus ketamine combined with morphine. It is difficult to determine if the reported difference in effectiveness is due the combination of ketamine and morphine or ketamine alone.

Observational studies

There have been numerous non-randomised publications reporting use of ketamine in the prehospital setting.[47–69] The vast majority comprise retrospective reviews of ketamine administration, some of which compare efficacy with other drugs. Indications for use included analgesia,[47,50–56,58,60–62,75] procedural sedation,[51,53,56,66] rapid sequence induction[48,49] and management of acute behavioural disturbance/excited delirium.[63–65] Reported outcomes include frequency of use, success rates across the different indications and incidence of adverse/side effects.

Among those studies reporting ketamine analgesia, the majority suggest that ketamine is as effective or better than morphine. Multiple studies further attest to the safety profile of ketamine across a range of indications and doses. Although these data are broadly supportive of ketamine, it is essential to note that they are observational in nature, limiting the conclusions that can be inferred. Furthermore, there is significant heterogeneity across the studies that were conducted. Few involved UK EMS systems and administration by critical care paramedics (CCPs) or doctors was common, sample sizes were small, with significant variation in the types of patients enrolled and dosages administered. These data are therefore insufficient to reliably inform wider Ambulance Service practice in the UK.

Systematic reviews or meta-analyses

We identified a small number of systematic reviews that included several of the observational studies identified above. It should also be noted that a small proportion of studies were common across the systematic reviews despite some variation in the objectives of the reviews. A 2011 systematic review included 6 studies, involving 340 patients, 2 of which were randomised trials.[71] Three of the included studies reported the effectiveness of ketamine analgesia and five reported side effects associated with ketamine administration. The authors concluded that ketamine was at least as effective as an opiate alone and does not increase the frequency or intensity of side effects.

A 2020 systematic review identified 10 studies, involving 2224 patients, 3 of which were randomised trials.[70] The authors reported three distinct groupings of study – those describing efficacy of ketamine without any comparator group, efficacy of ketamine alone versus ketamine with morphine and finally efficacy of ketamine versus any other analgesic or placebo. They concluded there was low-grade evidence that ketamine offered a safe and effective analgesia when used as the only analgesic, and low-grade evidence that it was as effective as alternative opioid options. They further reported that there was moderate evidence that coadministration of ketamine with morphine may improve analgesic efficacy and reduce morphine requirement.

Sandberg *et al.*[72] conducted a meta-analysis of 8 studies, involving 2760 patients, 5 of which were randomised trials. The authors reported 5 distinct groupings of study – those describing efficacy of ketamine versus opioid, efficacy of ketamine alone versus ketamine and morphine, ketamine bolus versus ketamine infusion, intranasal ketamine and Entonox versus Entonox alone and finally ketamine versus no analgesia. They concluded that ketamine probably reduces pain more than opioids do and additionally does so with less nausea and vomiting but a higher risk of agitation.

Finally, Youseffardi *et al.*[73] conducted a meta-analysis of 7 studies, involving 1064 patients, 4 of which were randomised trials. The authors reported four distinct groupings of study – those describing efficacy of ketamine versus morphine, efficacy of ketamine alone versus ketamine and morphine, ketamine versus fentanyl, and finally ketamine versus placebo. They concluded that ketamine provides similar pain relief to opioid analgesics but had fewer side effects. They further asserted that ketamine plus morphine coadministration offered no advantage compared to administration of morphine alone.

Despite a reasonable number of publications describing the effectiveness of ketamine in the prehospital environment, high-quality evidence demonstrating superiority of ketamine to morphine is severely lacking. The most convincing evidence derives from the KETAMORPH study by Le Cornec *et al.*[43] which was published more recently than all of the identified reviews. However, this study may lack generalisability to the UK as it was conducted among a physician cohort rather than a paramedic cohort. This lack of evidence limits access to a potentially effective treatment. The PACKMaN study was conceived to address this issue.[76]

Rationale for PACKMaN

The most frequently administered drug for moderate to severe pain following trauma, in ambulance services, is morphine sulphate.[32,33] Morphine has several undesirable side effects including nausea, confusion, dizziness, drowsiness, respiratory depression, hypotension and arrhythmia that may limit its use.[77–80] This, and concerns about potential longer-term dependence, may limit effective use by paramedics.[23]

Ketamine has been proposed as an ideal prehospital analgesic agent due to its rapid onset of action, effective analgesia, favourable haemodynamic stability, and preservation of upper airway reflexes.[50] Ketamine has a distinct dose-response gradient in which small doses (< 0.5 mg/kg) provide an analgesic effect and large doses (> 2 mg/kg) an anaesthetic effect.[68] It exerts its effect by 'disconnecting' the thalamocortical and limbic systems, effectively dissociating the central nervous system from outside stimuli (e.g. pain, sight, sound).[81] Ketamine also stimulates the sympathetic nervous system and moderately increases heart rate and blood pressure. Ketamine does not normally affect respiration; patients breathe spontaneously and maintain airway reflexes.[66]

The prehospital environment can be unpredictable. Ketamine appears to have a wide margin of safety. Serious adverse outcomes have not been reported even though overdoses of 5–100 times the intended dose have been inadvertently administered, suggesting ketamine may also have additional benefits with respect to safety.[47] Finally, there is additional evidence to indicate that perioperative ketamine analgesia may prevent hyperalgesia, reducing the risk of developing persistent post-operative pain.[82,83] This suggests ketamine might be associated with a lower incidence of chronic pain post trauma.

Due to its rapid onset and favourable side-effect profile, ketamine is already used in many ambulance systems around the world.[52,55,71,84–86] However, in the UK ketamine is currently restricted for use by prehospital doctors and a limited pool of specialist CCPs, targeted to the small number of cases needing critical care support.[53,87] This is primarily because there is little quality evidence of its effectiveness and safety as summarised above.

Trial overview

The PACKMaN trial protocol has previously been published.[88] Briefly, PACKMaN was a double-blind, individually randomised, parallel arm, controlled trial comparing ketamine and morphine in patients reporting severe pain following trauma. Eligible patients comprised those who had suffered an acute traumatic injury, were at least 16 years of age or over, reported a pain score of 7 or greater on a 0–10 NRS and, in the opinion of the attending paramedic, would normally require parenteral morphine for analgesia. Participating ambulance services included West Midlands Ambulance Service (WMAS) and Yorkshire Ambulance Service (YAS).

Approvals

The trial was sponsored by the University of Warwick. Ethical approval was granted by the West of Scotland Research Ethics Committee (REC) (20/WS/0126). The trial was registered with the International Standard Randomised Controlled Trial Number registry (ISRCTN14124474) on 22 October 2020 and the European clinical trials database (EudraCT 2020-000154-10).

Eligibility

Excluded patients included known or suspected pregnancy (both ketamine and morphine cross the placental barrier), those unable to articulate severity of pain using the 0–10 NRS (prerequisite for consideration of eligibility), any patient lacking capacity due to a reason other than pain (unable to reliably obtain assent to participation), known prisoners (require additional approvals and safeguards that would have delayed recruitment. We did not anticipate there would be a high proportion of prisoners, so made a pragmatic decision to exclude this population in order to deliver a more cost-effective trial. This mirrors practice

in many clinical trials) or any patient who declined participation. In addition, patients who received parenteral ketamine or opioid analgesia prior to randomisation, or who had a contraindication to either drug, were also excluded.

Trial intervention

The trial drugs were supplied in 2 ml glass ampoules containing either 15 mg of ketamine hydrochloride or 10 mg of morphine sulphate. Drug ampoules were identical in appearance. The trial drug was prepared by diluting one ampoule of trial drug (either ketamine or morphine) with 9 ml of 0.9% sodium chloride in a 10 ml syringe. The trial drug was then administered by slow IV or intraosseous (IO) injection, titrated to effect over 5 minutes. The paramedic then waited a further 5 minutes for the drug to exert an effect. If after 5 minutes the patient still reported pain, the paramedic was able to prepare a second syringe of trial drug and administer it in the same manner. The maximum cumulative volume of trial drug that could be administered was 20 ml. This equates to a maximum dose of either 20 mg of morphine or 30 mg of ketamine.

Outcome measures

The primary outcome measure was the Sum of Pain Intensity Difference (SPID) score. SPID is advocated by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials guidance,[89] and defined as difference in pain intensity per unit of time.[90] Pain intensity was measured using the 0–10 NRS, documented by the attending paramedic. Time was assessed as the interval, in hours, between each NRS score. Our trial was powered to detect a 1-point difference in SPID score to confirm superiority. Secondary outcomes, including the time points at which they were measured, are reported in the *Table 1*.

Trial data were extracted from routinely collected electronic patient care records by research paramedics and uploaded to the trial database using a predefined data entry template. Ambulance services amended their respective electronic patient care records a-priori to collect trial specific outcomes, such as Global Impression of Change. No supplemental data collection instrument was completed by participating paramedics.

All analyses were conducted using the intention to treat principle. The morphine group was the reference group for the analysis. The primary analysis was effectiveness of pain relief from randomisation to arrival at hospital as measured by SPID score (using a 0–10 numerical rating scale). All planned analyses are detailed in the Statistical and

TABLE 1 Secondary outcomes and time points for measurement

	Time point			
Secondary outcome	**Baseline/prehospital**	**After hospital arrival**	**3 months**	**6 months**
Vital signs	✓			
TOTPAR	✓			
Side effects and AEs	✓	✓	✓	✓
Time to perceptible analgesia	✓			
Time to meaningful analgesia	✓			
Time to peak analgesia	✓			
Duration of analgesia	✓			
Patient global impression of change	✓			
Rescue analgesia	✓			
Resource use	✓	✓	✓	✓
Quality of Life – EQ-5D-5L			✓	✓
Questionnaire – BPI-SF			✓	✓
Questionnaire – CSRI			✓	✓

AEs, adverse events; BPI-SF, Brief Pain Inventory – Short Form;[92] CSRI, clinimetric self-reported instrument; EQ-5D-5L, EuroQol-5 Dimensions, five-level version;[91] TOTPAR, Total Pain Relief.[89] Reproduced from Smyth *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The table above includes minor additions and formatting changes.

Health Economic Analysis Plans (see *Report Supplementary Material 1*).

Research paramedics contacted participants who consented to long-term follow-up. Quality of life (EQ-5D-5L) and chronic pain [Brief Pain Inventory – Short Form (BPI-SF)] assessments were completed by research paramedics, either face to face, or virtually on request of the patient.

Results

PACKMaN recruited its first patient on 10 November 2021 and achieved its recruitment target on 31 May 2024. During the course of the trial, we screened 938 potentially eligible patients, from whom 449 were recruited – 219 (49%) were randomised to the ketamine arm and 230 (51%) to the morphine arm (*Figure 1*). Baseline characteristics [age, gender, ethnicity, patient-reported weight, initial pain score, mechanism of injury, systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, oxygen saturations, Glasgow Coma Score (GCS), type of injury sustained, and body part injured] were similar across the two treatment arms (*Table 2*). The mean age of the included population was 63.6 years [standard deviation (SD) 21.7]. The mean cumulative dose of ketamine administered was 17.7 mg (SD 7.6 mg) while the mean dose per kilogram was 0.24 mg/kg (SD 0.11 mg/kg). The mean cumulative dose of morphine administered was 12.5 mg (SD 5.0 mg) and the mean dose per kilogram was 0.17 mg/kg (SD 0.08 mg/kg). All patients received the trial intervention via the IV route. No patients received drugs via the IO route.

We also reviewed those patients screened for inclusion who were not randomised. This group primarily comprised patients who were not eligible for consideration, for example pregnant patients, but also included cases of missed enrolments. Missed enrolments were patients who were eligible for the trial but not randomised for some reason. For example, this could occur if the trial paramedic encountered two eligible patients in a single shift. Trial paramedics only carry a single drug pack that, if it has already been opened, cannot be reused. We reviewed the explanations for all missed enrolments.

The reasons for missed enrolment are shown in *Table 3*, 220 potential participants were missed due to paramedic not carrying a study drug pack, 2 participants were missed due to the pack being used previously on shift, and 748 participants were missed due to other reasons. Supplementary reasons for ineligibility that are not included in the Consolidated Standards of Reporting Trials (CONSORT) diagram are shown in *Table 4*. These are 9536 patients being under the age of 16, 65,241 patients reporting a pain score below 7, 2935 patients where IV access was not obtained, and 29,860 patients where the attending paramedic determined patient did not require IV morphine or equivalent.

Principle finding

We found that ketamine was not superior to morphine. The SPID score for ketamine was 3.5 (SD 2.8) while the SPID score for morphine was 3.4 (SD 3.0) [adjusted mean difference (MD) 0.1, 95% CI −0.4 to 0.6; $p = 0.7$]. This finding demonstrates that the overall analgesic effects of both drugs were similar from randomisation through to handover at hospital.

Secondary findings

Broadly speaking, our secondary outcomes can be grouped into ambulance and initial hospital outcomes, secondary hospital outcomes, safety outcomes, 3-month outcomes and 6-month outcomes (*Table 5*). With respect to ambulance and initial hospital outcomes we found no significant difference between drugs except with respect to time to analgesia, duration of analgesia, likelihood of achieving 'very much pain relief', blood pressure and oxygen saturations. Ketamine had a shorter interval to 'much relief' [hazard ratio (HR), 1.3 (1.1 to 1.7); $p = 0.01$] and a shorter interval to 'very much relief' [HR, 1.4 (1.1 to 1.8); $p = 0.01$]. Ketamine was also more likely to produce 'very much relief' [odds ratio (OR), 1.6 (1.1 to 2.3); $p = 0.02$]. On the other hand, morphine was more likely to produce longer lasting analgesia [HR, 1.3 (1.0 to 1.5); $p = 0.01$], to reduce blood pressure [MD, 4.6 (0.9 to 8.2); $p = 0.01$] and to lower oxygen saturations [MD, 0.6 (0.2 to 0.9); $p < 0.01$].

There were no significant differences between drugs with respect to secondary hospital outcomes including number of CT scans, proportion of patients admitted to hospital, proportion of patients admitted to critical care or duration of hospital stay.

Our long-term follow-up did not identify any significant differences between ketamine and morphine. However, we did identify a relationship between patients who still reported moderate or severe pain on hospital arrival (irrespective of which treatment they received), and subsequently experiencing chronic pain. We defined chronic pain as pain that persisted 3 months after the initial injury, as per the IASP.[93,94] It is currently unclear if inadequate pain management was a causative factor in developing chronic pain or merely a correlating factor, for example both suboptimal pain control and chronic pain might be influenced by injury severity. Further research will be

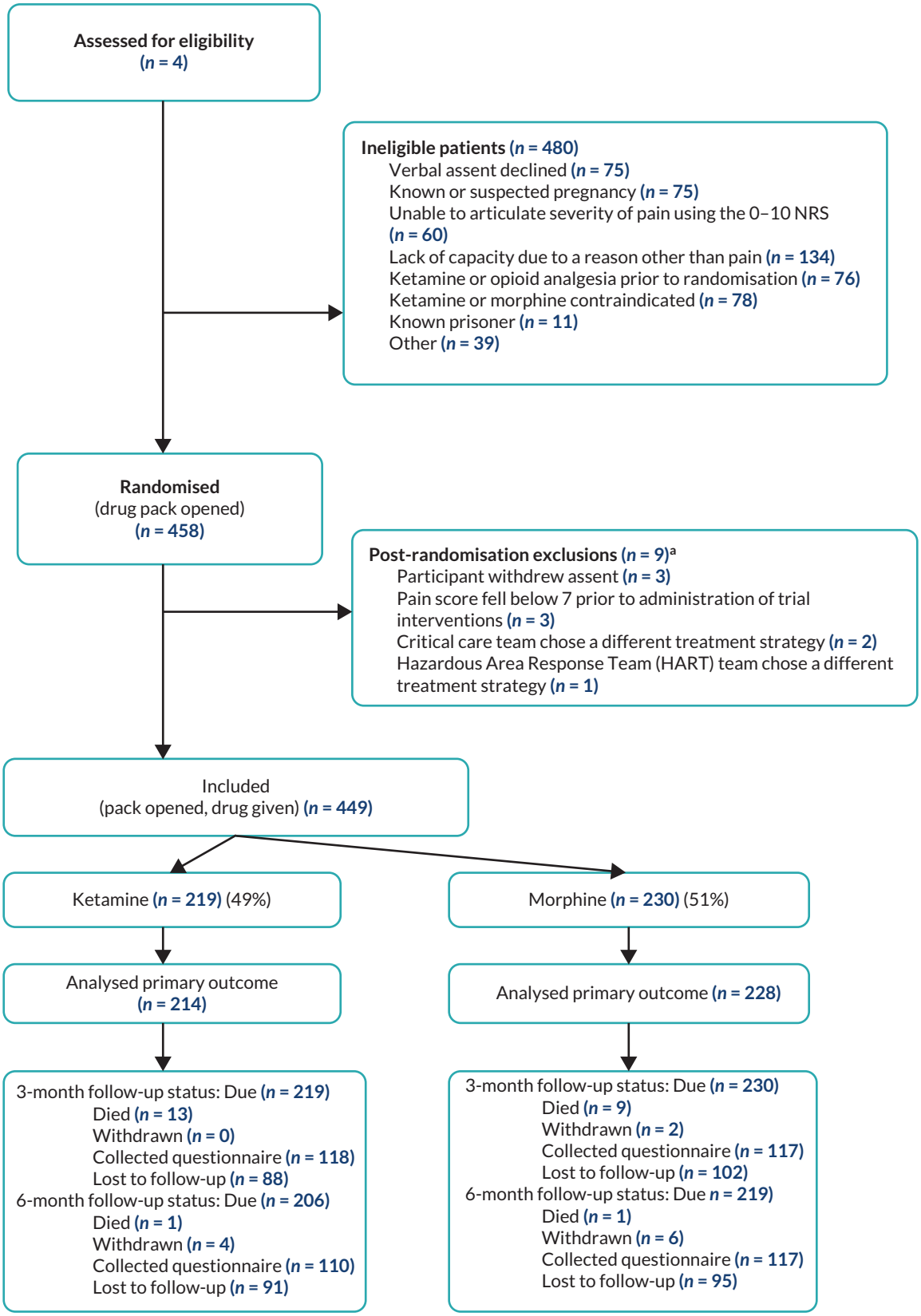


FIGURE 1 Trial profile. a, Participant where drug pack was opened but participant was excluded from trial prior to investigational medicinal product being administered. Reproduced with permission from Smyth *et al.*[1] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) licence, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes.

TABLE 2 Participant baseline characteristics

	Ketamine (*n* = 219)	Morphine (*n* = 230)
Age (years), mean (SD)	64.0 (21.3)	63.2 (22.1)
Gender, N (%)		
Male	102 (47%)	106 (46%)
Female	117 (53%)	124 (54%)
Ethnicity,[a] N (%)		
White	98 (45%)	108 (47%)
Black	–	–
Mixed	–	–
Any other ethnic group	2 (1%)	–
Asian	-	1 (< 1%)
Ethnicity not documented	118/218 (54%)	119 (52%)
Weight (kg), mean (SD)	75.2 (17.5)	77.6 (19.1)
Initial pain score (0–10),[a] mean (SD)	8.8 (1.3)	8.9 (1.2)
Mechanism of injury,[a] N (%)		
Blunt trauma	215 (98%)	227 (99%)
Penetrating trauma	3 (1%)	2 (1%)
Burn	1 (< 1%)	0
Injuries sustained, N (%)		
Fracture/dislocation	193 (88%)	210 (91%)
Soft tissue injury	72 (33%)	69 (30%)
Wound/laceration	23 (11%)	34 (15%)
Body part/region injured, N (%)		
Head	16 (7%)	21 (9%)
Neck	9 (4%)	15 (7%)
Chest and back	44 (20%)	43 (19%)
Abdomen	6 (3%)	6 (3%)
Pelvis	68 (31%)	62 (27%)
Upper limbs	43 (20%)	60 (26%)
Lower limbs	153 (70%)	149 (65%)
Vital signs		
Systolic blood pressure (mmHg), mean (SD)	145.6 (24.0)	147.8 (27.8)
Diastolic blood pressure (mmHg), mean (SD)	82.0 (15.2)	84.6 (16.2)
Heart rate (bpm), mean (SD)	81.8 (16.3)	83.4 (16.2)
Respiratory rate (bpm),[a] mean (SD)	19.2 (3.4)	19.5 (4.3)

continued

TABLE 2 Participant baseline characteristics (*continued*)

	Ketamine (*n* = 219)	Morphine (*n* = 230)
Oxygen saturations (%),[a] mean (SD)	97.3 (2.5)	96.8 (3.4)
GCS,[a] N (%)		
15	214 (99%)	227 (100%)
14	2 (1%)	0
13	0	0
12	1 (< 1%)	1 (< 1%)
11 or lower	0	0

a Absolute numbers.

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TABLE 3 Reasons for missed enrolment, per ambulance service and total

Missed enrolment reasons	YAS	WMAS	Total
Paramedic trained but not carrying pack	220 (99%)[a]	0	220 (24%)
Paramedic trained but pack used previously on shift	2 (1%)	0	2 (< 1%)
Other reason	0	709 (100%)	709 (76%)

a Due to limited drug supply, rollout of the trial to several YAS ambulance stations was delayed, consequently there were multiple stations where paramedics were trained to recruit patients to the trial, but no trial drugs were available.

Note
Percentages are based within each ambulance service.

TABLE 4 Reasons for ineligibility, per ambulance service and total

Eligibility criteria	YAS	WMAS	Total
Under 16 years of age	1 (< 1%)	9535 (9%)	9536 (9%)
Patient reported pain score is below 7	55 (18%)	65,186 (60%)	65,241 (60%)
IV and IO access not obtained	1 (< 1%)	2934 (3%)	2935 (3%)
Paramedic determined patient did not require IV morphine or equivalent	4 (1%)	29,856 (28%)	29,860 (28%)
Known or suspected pregnancy	0	7 (< 1%)	7 (< 1%)
Unable to articulate pain severity	6 (2%)	54 (< 1%)	60 (< 1%)
Lack of capacity due to reason other than pain	74 (25%)	60 (< 1%)	134 (< 1%)
Ketamine or opioid analgesia prior to randomisation	41 (14%)	35 (< 1%)	76 (< 1%)
Known contraindication to either ketamine or morphine, per SmPC	19 (7%)	59 (< 1%)	78 (< 1%)
Patient declined participation	57 (19%)	18 (< 1%)	75 (< 1%)
Known prisoner	4 (1%)	7 (< 1%)	11 (< 1%)
Other	39 (13%)	0	39 (< 1%)

SmPC, summary of product characteristics.

Notes
Percentages are based within each ambulance service.
The difference in numbers reported between services relate to how the respective services approached screening. WMAS screened all trauma patients, whereas YAS screened only potentially eligible patients.

TABLE 5 Primary and secondary outcomes

	N	Ketamine (*N* = 219)	*N*	Morphine (*N* = 230)	Adjusted estimate (95% CI); *p*-value
Primary outcome					
SPID, mean (SD)	214	3.5 (2.8)	228	3.4 (3.0)	MD, 0.1 (−0.4 to 0.6); 0.70
Secondary outcomes					
TOTPAR, mean (SD)	214	1.4 (1.1)	228	1.4 (1.2)	MD, 0.03 (−0.2 to 0.2); 0.75
Achieved 'minimal relief' analgesia, *N* (%)	214	195 (91%)	228	208 (91%)	OR, 1.0 (0.5 to 2.0); 0.96
Minutes to 'minimal relief',[a] median (IQR)	195	6 (3–15)	208	8 (4–14)	HR, 1.1 (0.9 to 1.3); 0.32
Achieved 'much relief', *N* (%)	214	155 (72%)	228	147 (64%)	OR, 1.5 (0.99 to 2.2); 0.06
Minutes to 'much relief',[a] median (IQR)	155	11 (6–25)	147	15 (7–31)	HR, 1.3 (1.1 to 1.7); 0.01
Achieved 'very much relief', *N* (%)	214	122 (57%)	228	105 (46%)	OR, 1.6 (1.1 to 2.3); 0.02
Minutes to 'very much relief',[a] median (IQR)	122	15 (6–33)	105	23 (10–37)	HR, 1.4 (1.1 to 1.8); 0.01
Minutes to peak analgesia,[a] median (IQR)	204	18 (8–36)	217	25 (10–43)	HR, 1.2 (0.96 to 1.4); 0.12
Duration (minutes) of analgesia,[a] median (IQR)	214	35 (22–51)	228	42 (26–57)	HR, 1.3 (1.0 to 1.5); 0.01
Required rescue analgesia, *N* (%)	219	1 (< 1%)	230	0	–
Final pain score < 4/10, *N* (%)	218	89 (41%)	228	86 (38%)	OR, 1.1 (0.8 to 1.6); 0.59
Minutes from arrival to drug administration, median (IQR)	218	31.5 (23–41)	228	30.5 (23–42)	MD, −0.5 (−4.3 to 3.4); 0.82
Minutes from drug administration to hospital arrival, median (IQR)	219	50 (36–63)	230	51 (35–67)	MD, −1.8 (−6.4 to 2.8); 0.45
Global impression of change*[b] *N	***216***		***225***		***OR, 1.0 (0.7 to 1.3); 0.78***
Very much improved *N* (%)		63 (29%)		64 (28%)	
Much improved *N* (%)		83 (38%)		82 (36%)	
Minimally improved *N* (%)		51 (24%)		62 (28%)	
No change *N* (%)		16 (7%)		17 (8%)	
Minimally worse *N* (%)		1 (< 1%)		0	
Much worse *N* (%)		1 (< 1%)		0	
Very much worse *N* (%)		1 (< 1%)		0	
Vital signs[c]					
Systolic blood pressure (mmHg), mean (SD)	216	149.2 (25.0)	225	143.1 (26.4)	MD, 4.6 (0.9 to 8.2); 0.01
Diastolic blood pressure (mmHg), mean (SD)	216	83.2 (15.0)	225	81.2 (15.1)	MD, 1.4 (−0.6 to 3.4); 0.18
Pulse rate (bpm), mean (SD)	216	80.2 (15.5)	224	81.7 (16.1)	MD, −1.6 (−4.1 to 0.8); 0.20
Respiratory rate (bpm), mean (SD)	214	18.3 (2.7)	225	18.6 (3.7)	MD, −0.1 (−0.7 to 0.4); 0.65
Oxygen saturations (%), mean (SD)	215	97.2 (2.6)	225	96.5 (3.3)	MD, 0.6 (0.2 to 0.9); < 0.01
GCS, mean (SD)	209	14.9 (0.4)	219	15 (0.2)	OR, 0.7 (0.2 to 2.5); 0.56

continued

TABLE 5 Primary and secondary outcomes (*continued*)

	N	Ketamine (*N* = 219)	*N*	Morphine (*N* = 230)	Adjusted estimate (95% CI); *p*-value
Hospital stay					
ED length of stay (minutes), mean (SD)	191	561.4 (355.8)	189	572.6 (371.8)	MD, −14.3 (−86.6 to 57.8); 0.70
Admitted – hospital, *N* (%)	206	133 (65%)	210	129 (61%)	OR, 1.1 (0.7 to 1.8); 0.59
Admitted – critical care, *N* (%)	133	4 (3%)	129	1 (1%)	OR, 6.7 (0.7 to 67.5); 0.11
CT scan usage (*N*)	190		191		
Patients scanned, *N* (%)		63 (33%)		77 (40%)	OR, 0.7 (0.5 to 1.1); 0.14
Scans performed (*N*)		178		181	
Scans per patient, mean (SD)		2.8 (2.8)		2.4 (2.2)	MD, 0.4 (−0.4 to 1.2); 0.33
Chronic pain					
BPI-SF (3 months) (*N*)	118		118		
Overall pain severity, mean (SD)	114	4.3 (2.3)	116	4.3 (2.4)	MD, −0.01 (−0.6 to 0.6); 0.98
Worst pain, mean (SD)	114	5.7 (2.9)	116	5.8 (3.1)	MD, −0.1 (−0.9 to 0.7); 0.82
Least pain, mean (SD)	114	3.0 (2.3)	112	2.9 (2.2)	MD, 0.1 (−0.5 to 0.7); 0.75
Average pain, mean (SD)	113	4.5 (2.4)	111	4.5 (2.4)	MD, 0.1 (−0.6 to 0.7); 0.86
Pain now, mean (SD)	114	3.9 (2.8)	111	3.7 (2.8)	MD, 0.2 (−0.5 to 0.9); 0.60
Pain interference, mean (SD)	115	4.4 (2.8)	113	4.9 (3.0)	MD, −0.5 (−1.2 to 0.3); 0.21
BPI-SF (6 months) (*N*)	110		118		
Overall pain severity, mean (SD)	106	4.0 (2.6)	114	4.0 (2.4)	MD, 0.1 (−0.6 to 0.7); 0.77
Worst pain, mean (SD)	106	5.2 (3.2)	114	5.4 (3.2)	MD, −0.1 (−1.0 to 0.7); 0.75
Least pain, mean (SD)	106	3.0 (2.5)	114	2.8 (2.3)	MD, 0.2 (−0.4 to 0.8); 0.52
Average pain, mean (SD)	105	4.3 (2.8)	113	4.3 (2.7)	MD, 0.1 (−0.6 to 0.8); 0.80
Pain now, mean (SD)	106	3.5 (2.8)	114	3.4 (2.6)	MD, 0.2 (−0.5 to 0.9); 0.53
Pain interference, mean (SD)	104	4.2 (2.9)	115	4.0 (2.9)	MD, 0.2 (−0.6 to 1.0); 0.61

ED, emergency department; IQR, interquartile range; TOTPAR, Total Pain Relief.
a Totals shown excludes censored participants and participants with missing data.
b Proportional odds assumption is not violated.
c These outcomes have been modelled using a mixed effect model.

Notes
BPI-SF is a scale of 1–11 where the higher score indicates more pain, overall pain severity is an average of these four questions, pain interference is an average of other questions on the BPI form about how pain interferes with everyday life.
Rescue analgesia is administration of open label ketamine or morphine before hospital arrival.
For the SPID and TOTPAR, a higher score indicates a better outcome.

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required to establish if adequate prehospital analgesia has a protective effect against developing chronic pain.

Finally, the health economic analysis estimated mean (SD) observed NHS and Personal Social Services costs at £5191 (£3155) in the ketamine arm versus £5143 (£3897) in the morphine arm (MD: £47; $p = 0.926$) over 6 months. Mean (SD) observed quality-adjusted life-year (QALY) estimates were 0.309 (0.10) versus 0.293 (0.010), respectively (MD: 0.016; $p = 0.273$) over this time horizon. However, missing data made the interpretation of results difficult, with follow-up complete in only about half of

participants. The base case (imputed) analysis generated an incremental cost of −£117 (95% CI −£849 to £597) and incremental QALYs of 0.025 (95% CI 0.010 to 0.041), indicating a 92–96% probability of cost-effectiveness at cost-effectiveness thresholds of £20,000 and £30,000 per QALY. However, a sensitivity analysis using observed data only (without imputation), generated an incremental cost of £233 (95% CI −£783 to £1216) and incremental QALYs of 0.016 (95% CI −0.013 to 0.044), indicating a substantially lower 54–62% probability of cost-effectiveness.

Safety and compliance

All adverse events (AEs) and serious adverse events (SAEs) were recorded, analysed and findings reported to the independent Data Monitoring Committee. An AE was defined as any untoward medical occurrence in a participant who received a trial-related drug. All cases where participants experienced notable drug side effects, for example hypotension, were recorded as AEs. An SAE was defined as an AE that fulfilled one or more of the following criteria:

- Resulted in death.
- Was immediately life-threatening.
- Required prolongation of hospitalisation.
- Resulted in persistent or significant disability or incapacity.
- Caused a congenital abnormality or birth defect.
- Required immediate intervention to prevent one of the above or was otherwise an important medical condition.

Throughout the study period 219 participants (47.8%) experienced at least one AE. The overwhelming majority of AEs were clinically predictable side effects of morphine or ketamine, with some patients experiencing more than one AE simultaneously, for example experiencing both respiratory depression and hypotension at the same time. If side effects were sufficient to warrant clinical intervention by the attending paramedic these were recorded as SAEs. Cumulative reported AEs by clinical category are reported in *Table 6*.

There was no overall difference in AE rates between the two drugs (OR 1.04, 95% CI 0.71 to 1.53; $p = 0.84$). However, there were three notable differences in the pattern of AEs. Patients receiving morphine were more likely to experience desaturation [OR, 0.4 (0.2 to 0.7); $p < 0.01$] and hypotension [OR, 0.2 (0.1 to 0.6); $p < 0.01$] than those receiving ketamine. Patients receiving ketamine were more likely to experience altered behaviour [OR, 8.6 (2.5 to 29.6); $p < 0.01$] than those receiving morphine.

In total 12 SAEs occurred (*Table 7*). No SAE was reportable to the regulating bodies.

There were 28 non-compliance events throughout the duration of the trial all of which were investigated by the Trial Steering Committee (TSC). Three of the non-compliance events were categorised as protocol violations, 24 were categorised as protocol deviations and one was revoked.

TABLE 6 Number of AEs by category reported by trial arm

Trial arm	Airway (*n*)	Respiratory (*n*)	Cardiovascular (*n*)	Neurologic (*n*)	Other (*n*)	Total (*n*)
Morphine	27	38	34	18	57	**174**
Ketamine	16	15	26	42	44	**143**
Total	**43**	**53**	**60**	**60**	**101**	**317**

TABLE 7 Serious adverse events

	Relationship to trial activity?		
Nature of SAE	Unrelated	Potentially related	Probably related
Death	3	0	0
Immediately life-threatening problem	2[a]	2	0
Prolonged hospitalisation	2	0	0
Persistent or significant disability or incapacity	0	0	0
Congenital abnormality or birth defect	0	0	0
Required immediate intervention to prevent one of the above or was otherwise an important medical condition	2[a]	2	3

a Duplicate cases where immediate intervention was required for an immediately life-threatening problem.

The three protocol violations comprised a patient randomised despite their injury being 3 days old (for which they had been prescribed opioids), late reporting of a desaturation event (this event was appropriately managed by the recruiting paramedic) and failure of Warwick statistics team to ensure all statistical code was independently reviewed by a second statistician.

The revoked non-compliance event involved a drug pack being appropriately opened by the participating paramedic, but the patient changed their mind before the trial drug ampoule was opened. The participating paramedic subsequently signed the drug pack back into the stores at the end of the shift. However, because the drug pack seal was broken, the pack should have been removed from circulation and returned to central stores for disposal as per local procedures for unused ampoules. There were no serious breaches. The 24 protocol deviations are summarised in *Table 8*.

Interpreting the findings

Severe pain following trauma is a common presenting complaint for paramedics. Irrespective of which treatment was provided, 6 out of every 10 patients were still experiencing moderate or severe pain when they arrived at the hospital. This finding indicates that prehospital pain management remains suboptimal and further improvement is required. Our study demonstrated that ketamine can be safely used by paramedics and that ketamine and morphine both provide very similar levels of pain relief. However, ketamine does appear to offer some clinically important advantages over morphine:

1. Ketamine works slightly quicker than morphine.
2. Patients who receive ketamine are more likely to experience much improvement in pain than those patients who receive morphine.
3. Patients who receive ketamine are also more likely to experience very much improvement in pain than those patients who receive morphine.
4. Patients who receive ketamine are less likely to experience respiratory depression than those patients who receive morphine.
5. Patients who receive ketamine are less likely to experience hypotension than those patients who receive morphine.

However, ketamine also has some disadvantages over morphine that need to be considered:

1. Ketamine does not last for as long as morphine.
2. Patients who receive ketamine are more likely to experience adverse behavioural reactions than patients who receive morphine.

These characteristics need to be considered in the round, and in the context of the entire patient journey. Early control of pain favours the use of ketamine. Similarly, ketamine is likely to be a more suitable choice for any patient who presents with, or is at risk of developing, hypotension or dyspnoea. However, this preference must be balanced against the challenge of providing frequent 'top-ups' as ketamine has a shorter duration of action, and therefore its' effect 'wears off' more rapidly. This may be particularly important during prolonged or difficult extrications, where delays to administering such 'top-ups' are more likely to occur, or during ambulance

TABLE 8 Protocol deviations by category

Site	Eligibility and randomisation		Intervention	IMP			Informed consent	Follow-up data not collected within timescale window	Data	Safety reporting	Other event	Total
	Ineligible patient	Other		Overdose	Under dose	Other						
WMAS	1	–	2	–	–	–	–	–	2	–	6	**11**
YAS	2	–	1	–	–	3	–	–	1	–	1	**8**
WCTU	–	–	–	–	–	–	–	–	3	–	–	**3**
ModeP	–	–	–	–	–	–	–	–	–	–	1	**1**
WPrint	–	–	–	–	–	–	–	–	–	–	1	**1**
Total	**3**	–	**3**	–	–	**3**	–	–	**6**	–	**9**	**24**

IMP, investigational medicinal product; ModeP, ModePharma; WCTU, Warwick Clinical Trials Unit; WPrint, Warwick Print Services.

transport where the treating paramedic may have many competing priorities.

Paramedics must also consider the likelihood of adverse behavioural reactions that might increase risks for the patient. This will be of particular importance in two contexts – first during extrication where an agitated patient might be at greater risk. For example, if they struggle against immobilisation there is a greater risk of exacerbating injuries. Secondly, in injuries associated with altered consciousness, such as head injuries, ketamine may increase the risk of missing important pathology. For example, a clinician may misinterpret agitation secondary to rising intracranial pressure to be a side effect of ketamine, missing a potential opportunity for intervention and leading to worse patient outcomes.

Finally, ketamine may offer longer-term benefits, with respect to both risk of chronic pain and cost-effectiveness. Although clinicians will undoubtedly believe these outcomes are important, their primary focus is likely to be what is occurring in front of them during the immediate patient encounter. Knowledge of longer-term benefits is likely to be reassuring, but unlikely to be the deciding factor influencing which drug to administer.

What does PACKMaN add to the evidence base?

PACKMaN makes several important contributions to the evidence base for prehospital ketamine in relation to acute severe pain following trauma. Most notably, PACKMaN establishes that sub-dissociative ketamine does not provide greater pain relief than morphine. This question was highlighted as a research priority in NICE guideline (NG39) *Major trauma: Initial assessment and management*.[95]

Previous trials have established that ketamine was not inferior to morphine.[42,43] However, non-inferiority studies do not inform the debate as to whether ketamine should be the primary analgesic in trauma. Only a superiority trial can help answer this question. We believe PACKMaN helps to inform this debate.

Our findings demonstrate that ketamine has several advantages over morphine in trauma. Although it does not provide greater pain relief than morphine, it works more rapidly than morphine, has fewer detrimental side effects and is safe when used by non-specialist paramedics. These characteristics support the argument that ketamine may be a better option for prehospital pain management in trauma.

Critically, our research has also highlighted that even though our control arm utilised the gold standard for trauma analgesia, and the intervention arm used the most promising alternative, the majority of patients (6 in 10) still reported moderate to severe pain at the end of the intervention period. Furthermore, one in three patients described minimal or no change in pain score by the time they arrived at hospital. This finding indicates that far too many patients experience ineffective pain management during the prehospital phase. There remains an urgent humanitarian need to establish a more effective approach to managing acute severe pain following trauma.

PACKMaN has also helped to inform an appropriate 'morphine equivalent' dose for ketamine. Previous studies have reported wide variation in the 'morphine equivalent' dose, ranging from 0.1 mg/kg[50] to 0.6 mg/kg.[55,57] Two recent reviews have suggested that an appropriate analgesic dose for ketamine is likely to fall in the range of 0.10 mg/kg[96] to 0.30 mg/kg.[72] Our results suggest that 0.15 mg/kg of ketamine provides analgesia equivalent to 0.1 mg/kg of morphine.

Chronic pain results in a significant health burden. Ineffective management of acute pain has been linked to the development of chronic pain.[28,29] Jennings *et al.* previously reported that they found no statistical difference in long term outcomes following their trial comparing ketamine and morphine versus morphine alone.[44] We too failed to identify any significant differences in chronic pain outcomes between ketamine and morphine in our study. However, we were able to demonstrate that, irrespective of drug received, if a patient still reported moderate or severe pain (pain score of 4/10 or higher) when they arrived at hospital, then there was an increased risk of developing chronic pain that persisted at 6 months post-injury. Although there are potential confounding reasons, this finding highlights a potential link between ineffective prehospital pain management and poor long-term patient outcomes.

We believe that PACKMaN is the first trial to report that sub-dissociative ketamine might be marginally more cost-effective than morphine. The base case analysis adopted by the economic evaluation showed that ketamine was associated with lower costs on average [−£117 (95% CI −£849 to £597)] and increased QALYs on average [0.025 (95% CI 0.010 to 0.041)]. This translated into a 92–96% probability that ketamine is cost-effective at cost-effectiveness thresholds of £20,000 and £30,000 per QALY. However, missing data made the interpretation of results difficult, with follow-up complete in only about

half of participants. This finding should therefore be interpreted with caution.

Historically, ketamine has been the preserve of doctors and CCPs working within prehospital critical care teams.[68] Operational use of ketamine by paramedics has required several safeguards (requirement for two clinicians capable of advanced airway management and availability of anaesthetic level monitoring) that have restricted its use.[53,87] Our findings suggest that ketamine can be safely used by operational paramedics and without the need for anaesthetic level monitoring. Indeed, our results indicate that ketamine may be a safer than the current gold-standard treatment, morphine, as it is associated with lower risk of adverse clinical side effects (desaturation and hypotension).

Strengths and weaknesses

A particular strength of our study is the double-blind nature of the trial. There are no previous blinded trials comparing ketamine and morphine. All previous trials have been open label trials which increases the risk of both reporting and confirmation bias. However, despite our best efforts to ensure participants were blinded, both ketamine and morphine have distinct side-effect profiles that may have enabled paramedics to correctly guess which drug had been administered, potentially unblinding them from treatment and increasing the risk of reporting and confirmation bias.

To assess the extent of this risk we performed a post hoc analysis to ascertain if paramedics were able to correctly guess which drug they had administered. Our analysis suggested that paramedics were not able to reliably identify which drug they had administered. However, if they had administered ketamine, they were more likely to correctly identify ketamine, than if they had administered morphine. Furthermore, our analysis utilised a representative sample of patients, not a purposefully selected sample of patients displaying typical drug-related side effects. It is therefore possible that some paramedics became unblinded when notable side effects associated with each drug occurred. It is unclear how this might have impacted reporting or how we could have mitigated against this possibility.

Our methodology required that patients had capacity to provide verbal assent to participate. Consequently, it is possible that we were unable to recruit the most severely injured patients, limiting the generalisability of our findings.

A potential omission from our study is the lack of sensitivity analysis addressing injury severity. We had planned to undertake such an analysis by referencing data collected by the National Major Trauma Registry (NMTR). The NMTR was previously the Trauma and Audit Research Network Database operated by the University of Manchester, on behalf of the NHS in England. All trauma units in England submit data for patients who sustain major trauma into the database. Entry into the database therefore implies the patient has suffered major trauma. We planned to classify our patients into two cohorts – those entered into the NMTR and those who were not, thereby dichotomising our patients into those with and those without major trauma. However, a cyberattack on the NHS infrastructure in 2023 severely disrupted collection of these data. Consequently, we were unable to obtain these data for a significant proportion of enrolled patients and therefore unable to undertake this sensitivity analysis in a reliable manner.

Take home message

Sub-dissociative ketamine is a safe and effective drug for use by all paramedics when treating patients reporting severe pain following trauma. It is a cost-effective, and potentially preferable alternative to morphine, that should be incorporated into the national paramedic formulary. Although our study was designed to ascertain if ketamine was superior to morphine, we believe our results suggest the two drugs are equally effective.

Reflections

COVID-19

The COVID-19 pandemic had several significant impacts upon our study:

- As ambulance services increased their response to meet the clinical needs of the community, they halted all research related activity as staff were re-deployed to maximise the availability of operational clinicians. This meant that PACKMaN was placed on hold for well over 12 months.
- As pandemic measures were eased and staff returned to the usual roles, there was significantly less interest from staff toward participating in research. Operational demands from COVID-19 left staff worn-out and many were disillusioned. Anecdotally, many staff reported needing to 'take a break' and there was little enthusiasm to take on what many perceived as 'additional work'.
- Our first batch of trial drugs had been manufactured just before the pandemic. These drugs had been released by the manufacturer with a minimum shelf life of 6 months. At the time we did not know if the shelf life would be extended because insufficient time

had passed for these quality assurance tests to be completed at that point. The trial was paused before we had the opportunity to commence recruitment. It was therefore possible that the drugs we had in stock might expire before we had the opportunity to use them. As it turned out, testing at the 12-month and 2-year milestones confirmed the drugs remained safe to use, and there was in fact adequate shelf life. However, this information was not available early in the trial causing uncertainty.

- COVID-19 also significantly impacted the supply chain for the investigational medicinal products (IMPs). Raw materials required to produce our trial medications were not obtainable. Consequently, we experienced many months of delay before our second batch of trial drugs was able to commence production. This delay significantly impacted how we delivered the trial. To ensure we did not run out of trial medications, training of paramedics was paused and roll-out of the trial to new stations was delayed. This maximised availability of trial drugs on ambulance sites that were already recruiting. Although our recruitment was initially ahead of projections due to rapid roll-out of training to paramedics, after many months of delays waiting for raw materials, we eventually fell behind on our recruitment projections. Our timelines had to be revised because of this delay.
- A further change implemented in response to efforts to reduce face-to-face contact, and therefore virus transmission, was how we obtained informed consent. This change is explained more fully in the learning section.

Engagement with partners and stakeholders

We had excellent engagement from our ambulance service partners throughout all stages of the study. We also received significant support from the Clinical Research Network (CRN). Most hospital sites were also willing to participate despite no direct funding for this activity. However, a small number of hospitals, one of which was a trauma unit, declined participation as there was no remuneration for data collection activities. Even following engagement via the CRN who highlighted their expectation that the hospital should collaborate, some trusts still refused to collect any data without financial compensation. This meant that some ambulance sites were unable to recruit patients to the trial as they commonly transported patients to hospitals that would not participate. This had a direct impact on recruitment with multiple eligible patients being excluded because the destination hospital had declined to facilitate data collection required for our secondary outcomes.

Challenge of conducting research in ambulance services

Conducting research in ambulance services is known to present a unique set of challenges. The workforce is distributed across a wide geographical area. Every participating paramedic must be trained to recruit patients and administer the trial intervention. Invariably the paramedic will be required to transport the intervention from the ambulance to the patient's side when they are already carrying a large amount of equipment. Patients may be acutely unwell, and the environment is often not conducive to seeking consent. Delivering training is complex as ambulances and their crew are constantly moving between areas. There is strong resistance to taking ambulances off-line to deliver trial-related training as this directly impacts the ambulance services ability to respond to patients. Delivering classroom-based training often requires backfill costs to cover operational needs. Research paramedics must cover many hospital sites, requiring multiple letters of access and travelling vast distances to collect what is often small amounts of data. Finally, the window of opportunity within which trial-related activity must take place can be very challenging requiring concurrent treatment, extrication from scene and transport all while continuing care and delivering trial interventions followed by hand-over of all relevant clinical and trial information to the hospital receiving staff. This places significant burden on participating paramedics who must do all of this by themselves without any assistance, from a research nurse for example.

There is also a narrow window within which consent can be obtained. Some studies such as PACKMaN may be suitable for a delayed consent model; however, others will require that consent is obtained during a very short duration clinical encounter. If consent is left to the hospital, then invariably the hospital will be credited with the accrual and the efforts of the ambulance personnel who delivered the intervention, go unrecognised. Additional investment to develop infrastructure supporting delivery of research within ambulance services would be very welcome.

Defining authorised health professionals

Current Health Research Authority (HRA) regulations require that the chief investigator for a clinical trial of an IMP (CTIMP) must be an *authorised health professional*.[97] An *authorised health professional* is defined in these regulations as a 'doctor, dentist, nurse or pharmacist'.[97] Other registered healthcare professionals, including all of the allied healthcare professions currently registered with the Health and Care Professions Council UK are not permitted to act as chief investigator for a CTIMP. Consequently, the current definition of an 'authorised health professional'

discriminates against allied health professionals and limits the research opportunities for these healthcare professionals. This restriction may stifle research as a result.

Consideration should be given to widening the list of 'authorised health professionals' to include any registered healthcare professional who is endorsed by their regulatory body as an independent prescriber. This would reduce discrimination and facilitate registered healthcare professionals, who are endorsed as independent prescribers, to act as chief investigators for CTIMP trials, provided they possess the requisite research and leadership skills.

Patient and public involvement

Patient and public involvement (PPI) contribution played an important role throughout the PACKMaN Trial to ensure the patient perspective was central to our study. The initial idea for our trial was presented to the after trauma PPI group, hosted by Barts Health NHS Trust at the Royal London hospital in London. The group were supportive of the need for this trial and encouraged us to develop our proposal more fully. We included a PPI member as co-applicant who contributed to developing the trial protocol and joined our Trial Management Group to oversee trial delivery. We also secured PPI representation on the TSC to ensure the patient perspective was present in trial oversight.

Because PACKMaN was an emergency care trial, patients may not have had full recollection of the events of the day that they were injured and recruited to the study. We engaged members of the Clinical Research Ambassador Group (CRAG) at University Hospital Birmingham NHS Foundation Trust to assist with development of patient facing study materials. In particular, CRAG members helped to develop our cover letters inviting participation, patient information leaflets, consent documents and trial results dissemination letters. Their input was critical to ensure all information conveyed to participants was clear, concise and sensitive in nature.

Patient and public involvement input also helped to shape our approach to follow-up by encouraging the use of remote engagement using web-based mobile phone technology to help widen participation. This was important in the context of the COVID-19 pandemic, where there were considerable concerns about face-to-face contact and the risk of virus transmission. Our approach of using a web-based consent form was recognised by the West Midlands CRN in their 2023 annual awards where the trial was awarded their 'innovation of the year' prize (see impact and learning section for further details).

Finally, our PPI members also collaborated on developing our plans for dissemination of trial results. They helped to design of the trial infographic to ensure that public-facing information was appropriate for a lay person.

Equality, diversity and inclusion

Minority ethnicities

There is considerable evidence to suggest that racial and ethnic disparities exist in the provision of emergency health care.[98] Furthermore, there are notable differences in how, and when, minority ethnic and socio-economic groups access emergency health care.[99] Existing prehospital literature demonstrates that patients from minority groups experience suboptimal pain management.[100,101] Addressing disparities in health care remains a priority for the NHS.[102]

Ambulance services are known to record significant amounts of data pertaining to cases and patients attended. Missingness of data within case records is generally very low.[103] However, data pertaining to ethnicity appear to be a notable exception to this finding. It is unclear why healthcare professionals fail to routinely document ethnicity data, as most clinicians recognise its value in improving equity of access.[104] It may, in part, be explained by language barriers that impede communication; however, it has also been suggested that patients might refuse consent to document ethnicity over fear of discrimination.[104] Bell and colleagues identified a paucity of evidence pertaining to UK practices and highlight a need for research to explore how ambulance services might help improve access to health care for minority groups.[105]

Within our trial, we note that 45.9% of patients were of White ethnicity. Patient care records indicated 0.2% of patients were of Asian ethnicity, while 0.4% of patients were documented to be of *any other ethnic group*. No patients were identified as being of Black or mixed ethnicity in the PACKMaN trial. However, in most included cases (52.8%), paramedics failed to document any ethnicity data. We do not have any insights into why this might be, beyond assuming clinicians feel uncomfortable asking patients to confirm their ethnicity. It may be that paramedics are confident in recognising those of White ethnicity, but not of other ethnicities. Missing ethnicity data in our sample means it was not possible to determine if patients from minority ethnicities were disadvantaged during their treatment.

Newly qualified paramedics

During a regular meeting with the TSC one of the TSC members asked if it was appropriate to ask newly qualified paramedics (NQPs) to participate in our trial, suggesting that it may be more appropriate to restrict participation to more experienced (band 6) paramedics. NQP describes recently qualified paramedics in their first 2 years of clinical practice as a paramedic. In this phase of their career, NQPs are remunerated at band 5 on Agenda for Change. During the NQP phase, these paramedics receive additional support via increased supervision and they must complete a work-based portfolio to aid clinical development. At the end of the 2-year NQP phase, the work-based portfolio is assessed and, if adequate, the NQP is upgraded to band 6, with less requirement for direct supervision.

The rationale provided by the TSC member addressed the fact that NQPs are inexperienced and my not have encountered many significant traumas during their training. Furthermore, trainee paramedics are not legally permitted to administer drugs (except those falling on schedule 7), so NQPs will also have limited experience of morphine, and almost no previous exposure to ketamine. It was suggested that NQPs may be working at maximum bandwidth without participating in the PACKMaN study and that the additional stress of using these controlled drugs could potentially result in undue stress on the paramedic and consequently, place patients at increased risk of harm.

The trial team felt this was a valid question and we agreed to approach our ambulance service partners for their insights. Alongside this we agreed to undertake an analysis of recruitment by stage of career (NQP vs. band 6 paramedic).

Initial feedback from our ambulance service partners indicated that NQPs should not be restricted from participating. Their justification for this was twofold:

1. Participation in PACKMaN was optional. No paramedics, NQP or band 6, were pressured into participation. Any paramedic who was not confident, or did not wish to take on the additional responsibilities of recruiting patients to the trial, simply declined participation in the required training. Any paramedic who did complete the training, but changed their mind, was entitled to withdraw from the trial without having to justify their decision. Finally, NQPs who were participating were enthusiastic about their participation, and wanted to recruit patients to the study.
2. If ketamine was shown to be effective, then future NQPs would be expected to use ketamine during their NQP phase. There would not be any phased introduction of ketamine, it would simply be an option in their toolbox. Ambulance services suggested that the PACKMaN study did not impose any new way of working that would place NQPs at greater risk.

Both ambulance services also highlighted that a significant proportion of participating paramedics were classified as NQP. Restricting participation to band 6 paramedics would adversely impact the ability of both ambulance services to recruit to the PACKMaN trial. However, this latter point, was merely an observation, and did not influence their rationale for including NQPs within the trial. Additionally, both ambulance services also commented that restricting participation to band 6 paramedics would deprive NQPs of a development opportunity.

Our analysis of recruitment by stage of career indicated that 32% of participating paramedics were classed as NQP (28% in WMAS, 36% in YAS). We found that there was no significant difference in non-compliance between NQPs and band 6 paramedics (3% vs. 1% respectively, OR 2.72, 95% CI 0.57 to 16.96; $p = 0.14$), AEs (47% vs. 50% respectively, OR 0.9, 95% CI 0.61 to 1.33; $p = 0.58$), or serious AEs (4% vs. 2% respectively, OR 2.74, 95% CI 0.72 to 12.57; $p = 0.09$).

Our analysis suggested that NQPs were able to safely recruit patients to the PACKMaN trial and that ambulance services were in favour of supporting NQP participation. We presented these findings to the TSC who were satisfied with our analysis and agreed that NQPs should continue to participate in the trial.

Impact and learning

Training

At the time of applying for study funding we proposed to deliver face-to-face training for participating paramedics. We did this because our ambulance partners felt this approach was safest for patients. Ketamine has historically been perceived as an anaesthetic drug. Its use up until this study had been restricted to doctors and advanced paramedics with additional critical care skills. There was concern that allowing non-specialist paramedics to administer ketamine without considerable classroom-based learning might place patients at increased risk of harm. Consequently, this was the approach to education that we proposed for our study.

However, COVID-19 forced us to reconsider this approach as all unnecessary face-to-face contact was discouraged. The obvious devolution of our intended approach was to a virtual classroom. This presented us with an opportunity consider how best to achieve this. We could have had an instructor deliver training via a virtual platform, or we could produce a single set of electronic learning resources that could be accessed by paramedics interested in participating.

Following discussion with our ambulance partners it was decided to produce a single set of electronic learning materials that any paramedic could access in their own time, to complete the required training. This reduced the burden of training delivery for the ambulance services during a particularly challenging time for the health services. A secondary benefit was a single training program that ensured consistency and avoided any confusion arising from mixed messages delivered by different instructors.

This approach to training appears to have been very effective. The number of trained paramedics rose much faster than our initial projections that were estimated assuming face-to-face delivery. Our records show that patients did not experience an increase in AEs, suggesting the move away from face-to-face delivery did not adversely impact patient safety. However, an unintended consequence of more participating paramedics was that we recruited patients at a faster rate and consequently consumed our stores of trial drugs much faster than we had anticipated. This did cause us some issues that we have addressed elsewhere in this synopsis.

Consent

Good clinical practice (GCP) is a set of internationally recognised ethical and scientific quality requirements that must be adopted when designing, conducting, recording and reporting clinical trials that involve people.[106] The Medicines for Human Use (Clinical Trials) Regulations 2004 require that all persons enrolled into clinical trials of medicinal products must provide informed consent, or a legal representative (LR) must provide consent on their behalf.[107] Implementation of Statutory Instrument 2006 No 2984, The Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006 introduced the legal framework that permitted enrolment of participants who lacked capacity to consent, into clinical trials in emergency situations.[108] The HRA and the Medicines and Healthcare Products Regulatory Agency have subsequently advocated a proportionate approach to the application of GCP when seeking consent from potential participants who are unable to consent.

It has been reported that acute pain disrupts cognitive function.[109,110] Cognitive function describes the ability to self-regulate one's thoughts, feelings and behaviours.[111] Consequently, it has been argued that acute pain might impede one's ability to provide informed consent.[112] Because patients enrolled into the PACKMaN trial were experiencing severe acute pain we sought to enrol patients without prior consent. This was appropriate as our trial meets the criteria established by the HRA:

1. Treatment needed to be given urgently.
2. It was necessary to take urgent action to administer the drug for the purposes of the trial.
3. It was not reasonably practicable to obtain consent from a LR.
4. The procedure was approved by an NHS REC.
5. Informed consent was sought from the patient or their LR as soon as possible.

We believe that the consent process adopted in PACKMaN was both effective, compliant with all relevant legislation and could serve as a model for future trials of this nature.

Consent process

Before recruiting any patient to the trial, the participating paramedic provided a potentially eligible patient with brief verbal information about the trial by reading predefined text from an aide memoire (see *Appendix 1*). The paramedic then advised the patient of their intention to enrol them into the PACKMaN trial and gave the patient the opportunity to decline participation. The paramedic documented the patient decision on the patient report form/clinical notes. If the patient declined further participation in the trial, then no further trial interventions were administered, and standard care was provided without prejudice. This general approach to consent has been adopted in previous prehospital trials without adverse effects.

If the patient did not decline participation, the paramedic proceeded to open the trial drug pack and randomise the patient into the trial. Clinical care was provided according to the trial protocol. When the patient was handed over at the receiving hospital the paramedic ensured they had the patients' contact details for a Research Paramedic to make further contact and obtain informed consent. On handover to the hospital, emergency department staff were notified that the patient had received trial medication. Informed consent was obtained by a research paramedic as soon as was practicable. This may have been after admission to a hospital ward or following discharge.

Traditionally, informed consent is obtained face to face to ensure the patient is provided with the appropriate patient information leaflets, is fully informed and to allow the patient the opportunity to ask whatever questions they might have. We did retain the option for face-to-face consent where the patient requested this. However, due to the restrictions imposed by the COVID-19 pandemic we also sought to ensure patients had the option to avoid face-to-face contact if they so wished.

We also developed an electronic consent process using Qualtrics software (Qualtrics, Provo, UT, USA), that mirrored the paper versions of patient information leaflets and consent forms, that the patient could access using a web browser on their mobile phone, electronic tablet or personal computer. There was, additionally, an option for the patient to complete the form via voice-call, with a research paramedic, who would enter the information into the online form on behalf of the patient, in real-time. This novel approach to obtaining informed consent remotely was recognised by the West Midlands CRN, being awarded their 'Innovation of the year' award in 2023. Furthermore, our Participant in Research Experience Survey indicated that our approach was successful with 80% of participants stating they would take part in research again (see *Appendix 2* for full report).

Impact of research participation

One of our ambulance service partners piloted the Visible Impact of Research Tool (VICTOR) tool to assess the impact of participating in the PACKMaN study. The report has been summarised below:

- Health benefit – patients received enhanced pain relief options and additional monitoring at 3 and 6 months post injury. Paramedics demonstrated that they were able to implement new clinical guidelines.
- Service and workforce impacts – participating paramedics received additional training, both in clinical aspects related to the trial and in relation to the research process.
- Research profile – there was increased interest in research from operational paramedics as well as building relationships with other organisations including hospitals and universities.
- Economic benefit – the trust received financial compensation to support trial delivery. This facilitated expansion of the research team and supported contract extensions for existing staff.
- The trial results may yield cost-savings in the future.
- Organisation influence and reputation – participating in PACKMaN raised the trust profile with external partners and of the research team within the trust.
- Knowledge generation and knowledge exchange – processes put in place to escalate any trial-related incidents were copied within the trust to appropriately escalate other clinical incidents not related to research. Trial results will generate new knowledge.
- General – monitoring put in place to monitor trial activities led to improved detection of non-trial-related clinical incidents. Improved communication. Increased willingness to participate in research.

Our trial has highlighted the capability of ambulance services to participate in research. PACKMaN was the first CTIMP of a controlled drug within ambulance services. CTIMPs represent a particular challenge for ambulance services as current legislation prohibits paramedics from possessing or administering many drugs under the controlled drugs legislation. PACKMaN has demonstrated that ambulance services have robust research and clinical governance processes to support the delivery of clinical trials of controlled drugs, where possession and administration by paramedics is permitted in law.

It has further helped to demonstrate that NQPs are both willing and able to deliver research interventions when managing complex patients with potentially life-changing injuries. NQPs were not overwhelmed and had sufficient bandwidth to simultaneously deliver both patient care and a research intervention.

Implications for decision-makers

The ideal prehospital analgesic is one that is cheap, effectively reduces pain intensity, is easy to administer, works rapidly, has few adverse side effects and is long lasting. No current analgesic option meets all these criteria.

The current gold standard is morphine. However, the onset of action for morphine is not ideal for prehospital clinicians, and it is prone to significant side effects that are undesirable, such as nausea, respiratory depression and hypotension. This may be an important consideration in the context of trauma.

PACKMaN has demonstrated that sub-dissociative ketamine does not provide greater pain relief than morphine. However, our results do indicate that ketamine provides equivalent pain relief to morphine, and it does so more rapidly than morphine. It is also less likely to precipitate potentially harmful side effects. Clinically ketamine may therefore be a better option than morphine in some contexts for example, hypotensive trauma. Our analysis also

suggests ketamine may be marginally more cost-effective than morphine in acute trauma.

For these reasons, we recommend that sub-dissociative ketamine should be included within the national paramedic formulary. This will require changes to relevant drugs legislation to allow paramedics to both possess and administer ketamine. Paramedic guidelines and training programs will also need to be amended to ensure the drug is safely administered, and appropriate governance procedures will also need to be put in place to oversee its use.

Guideline developers should take heed of the results of this trial. Most patients arrive at hospital still experiencing pain. Neither ketamine nor morphine alone effectively reduces acute pain from severe to mild. There may additionally be a link between acute pain management and development of chronic pain. Robust clinical guidelines should promote better pain management and reduce the risk of chronic pain.

There is inconsistency in current legislation concerning the scope of trainee health professionals with respect to drug administration. The Human Medicines Regulations 2012 currently limit drug exemptions to 'registered paramedics' only; however, drug exemptions for midwives include 'registered midwives and student midwives'. It would be prudent to consider amending such legislation to allow all regulated student health professionals to administer drugs, within their respective professional scope of practice, under the supervision of an appropriately registered professional.

Research recommendations

Our research indicates that 6 out of every 10 patients treated were still experiencing moderate or severe pain when they arrived at the hospital, despite receiving appropriate treatments. This finding highlights the need to improve management of acute severe pain by paramedics.

Further research will be required to identify the best performing analgesic, or combination of analgesics, that achieves rapid reduction in pain intensity without producing significant undesirable side effects. This research should encompass:

- Exploring drug doses – for example, the current recommended dose for morphine is 0.1 mg/kg. In our study, the cumulative dose of morphine administered was 0.17 mg/kg. Similarly, the recommended dose for ketamine is 0.1–0.3 mg/kg and in our study the cumulative administered dose was 0.24 mg/kg. Further research should establish if larger initial doses of analgesics provide greater analgesia without increasing side effects.
- Exploring the potential of loading doses. Many drugs require a loading dose to rapidly achieve therapeutic drug levels in the blood stream. Many clinicians do this when administering analgesia; however, current paramedic guidelines advocate for a slow titration to response. Front-loading the analgesic dose may help achieve more rapid relief in the often-short prehospital interval.
- Exploring other drug options such as fentanyl or diamorphine, which have the same benefits as morphine, but are faster acting.
- Exploring the effectiveness of drug combinations, such as ketamine and morphine combined.
- Exploring the efficacy of different drug routes, including buccal, intranasal and intramuscular drug administration.
- Our research highlighted that ketamine has a short duration of action and begins to wear off before the patient arrives at hospital. Additional research is required to determine if infusions or regular small boluses may help mitigate the short duration of action.

Our study identified a correlation between pain intensity on arrival at hospital and subsequently developing chronic pain. There is significant literature addressing the relationship between poor early pain management and developing chronic pain. However, most of these studies focus on surgical and cancer patients with some studies exploring the relationship between battlefield injuries and chronic pain. No literature exists defining a link between urban/civilian paramedic pain management and subsequent chronic pain issues. Although there are many possible reasons for our finding, it will be important to establish if adequately reducing pain intensity by the time of hospital arrival has a protective effect against developing chronic pain. There may, in addition, be a relationship between psychosocial factors and development of chronic pain that is worthy of further investigation.

Our research focused on paramedics delivering a treatment. We did not spend an extended period teaching paramedics how to assess pain. Evidence suggests that education interventions may help improve prehospital pain management.[113]

Conclusions

In this blinded randomised trial comparing sub-dissociative ketamine and morphine administered by paramedics, we found that ketamine was not superior to morphine for the management of acute severe pain following trauma. However, our trial suggests that ketamine is more likely to provide both meaningful and substantial pain relief and will achieve these effects more rapidly than morphine. Furthermore, morphine is more likely to precipitate both hypotension and desaturation, while ketamine is more likely to result in altered behaviour. These findings suggest ketamine is safe for use by paramedics and is likely to be a valuable addition to the paramedic formulary.

Additional information

CRediT contribution statement

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Patient data statement

The work contained in this report uses data provided by patients and collected by the NHS Ambulance Services as part of their care and support.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

The trial was approved by the West of Scotland REC on 01 September 2020 (20/WS/0126).

Information governance statement

The University of Warwick is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, The University of Warwick is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here: https://warwick.ac.uk/services/legalandcomplianceservices/dataprotection.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/KGTO6391.

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This synopsis was published based on current knowledge at the time and date of publication. NIHR is committed to being inclusive and will continually monitor best practice and guidance in relation to terminology and language to ensure that we remain relevant to our stakeholders.

Trial registration

This trial is registered as Current Controlled Trials ISRCTN14124474. PACKMaN was registered with the International Standard Randomised Controlled Trial Number registry (ISRCTN14124474) and the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT 2020-000154-10).

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Award publications

This synopsis provided an overview of the research award *A randomised controlled trial of Paramedic Analgesia Comparing Ketamine and MorphiNe in trauma (PACKMaN)*.

Other articles published as part of this thread are:

Smyth MA, Noordali H, Starr K, Yeung J, Lall R, Michelet F, *et al*. Paramedic analgesia comparing ketamine and morphine in trauma (PACKMaN): a randomised, double-blind, phase 3 trial. *Lancet Reg Health Eur* 2025;**53**:101265. https://doi.org/10.1016/j.lanepe.2025.101265

Khan KA, Smyth M, Perkins GD, Yeung J, Walker A, McLaren R, *et al*. Cost-effectiveness of paramedic administered ketamine compared to morphine for the management of acute severe pain from traumatic injury. *Cost Eff Resour Alloc* 2026;**24**:28. https://doi.org/10.1186/s12962-025-00712-x

Rosser A, Gunson I, Green Z, Lall R, Michelet F, Miller E, *et al*. Safety and compliance among newly qualified paramedics in a pre-hospital clinical trial of an investigational medicinal

product: a post hoc analysis of the PACKMaN study. *Br Paramed J* 2025;**10**(3):10–7. https://doi.org/10.29045/14784726.2025.12.10.3.10

For more information about this research, please view the award page (www.fundingawards.nihr.ac.uk/award/NIHR128086).

Additional outputs

Michelet F, Smyth R, Lall R, Noordali H, Starr K, Berridge L, *et al.* Randomised controlled trial of analgesia for the management of acute severe pain from traumatic injury: study protocol for the paramedic analgesia comparing ketamine and morphine in trauma (PACKMaN). *Scand J Trauma Resusc Emerg Med* 2023;**31**. https://doi.org/10.1186/s13049-023-01146-1

The following was still under review when this synopsis was published. The following preprint version is available for the reader; please be aware this may not have been peer reviewed:

Smyth MA, Noordali H, Starr K, Yeung J, Lall R, Michelet F, *et al.* Impact of ineffective prehospital analgesia on chronic pain outcomes. A secondary analysis of outcomes from the PACKMaN trial. *medRxiv* 2025. www.medrxiv.org/content/10.1101/2025.08.01.25332769v1

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List of supplementary material

Report Supplementary Material 1
Statistical analysis plan and health economic analysis plan

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/KGTO6391).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

The supplementary materials (which include but are not limited to related publications, patient information leaflets and questionnaires) are provided to support and contextualise the publication. Every effort has been made to obtain the necessary permissions for reproduction, to credit original sources appropriately, and to respect copyright requirements. However, despite our diligence, we acknowledge the possibility of unintentional omissions or errors and we welcome notifications of any concerns regarding copyright or permissions.

List of abbreviations

AE	adverse event
BPI-SF	Brief Pain Inventory – Short Form
CCPs	critical care paramedics
COVID-19	coronavirus disease 2019
CRAG	Clinical Research Ambassador Group
CRN	Clinical Research Network

CSRI	clinimetric self-reported instrument
CTIMP	Clinical Trial of an Investigational Medicinal Product
GCP	good clinical practice
GCS	Glasgow Coma Scale
HR	hazard ratio
HRA	Health Research Authority
IMP	investigational medicinal product
IO	intraosseous
IV	intravenous
LR	legal representative
MD	mean difference
NMTR	National Major Trauma Registry
NQP	newly qualified paramedic
NRS	Numeric Rating Scale
OR	odds ratio
PPI	patient and public involvement
QALY	quality-adjusted life-year
RCT	randomised controlled trial
REC	Research Ethics Committee
SAE	serious adverse event
SD	standard deviation
SmPC	summary of product characteristics
SPID	Sum of Pain Intensity Difference
TSC	Trial Steering Committee
VAS	visual analogue scale
WHO	World Health Organisation
WMAS	West Midlands Ambulance Service
YAS	Yorkshire Ambulance Service

References

1. Smyth MA, Noordali H, Starr K, Yeung J, Lall R, Michelet F, *et al.* Paramedic analgesia comparing ketamine and morphine in trauma (PACKMaN): a randomised, double-blind, phase 3 trial. *Lancet Reg Health Eur* 2025;**53**:101265. https://doi.org/10.1016/j.lanepe.2025.101265
2. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, *et al.* The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain* 2020;**161**:1976–82. https://doi.org/10.1097/j.pain.0000000000001939
3. American Academy of Pain Management. *Pain Management. A Practical Guide for Clinicians*. 6th edn. New York: American Academy of Pain Management; 2002.
4. Schug SA, Palmer GM, Scott DA, Halliwell R, Trinca J. *Acute Pain Management: Scientific Evidence*. Australia: Australian and New Zealand College of Anaesthetists Melbourne; 2020.
5. International Association for the Study of Pain. *Access to Pain Management: Declaration of Montreal*. 2011. URL: www.iasp-pain.org/advocacy/iasp-statements/access-to-pain-management-declaration-of-montreal/ (accessed 15 August 2024).
6. World Health Assembly. *Strengthening of Palliative Care as a Component of Comprehensive Care Throughout the Life Course*. WHA67.19; 2014.
7. Alonso-Serra HM, Wesley K; National Association of EMS Physicians Standards and Clinical Practices Committee. Prehospital pain management. *Prehosp Emerg Care* 2003;**7**:482–8.
8. Henderson T, Endacott R, Marsden J, Black S. Examining the type and frequency of incidents attended by UK paramedics. *J Paramed Pract* 2019;**11**:396–402.
9. Berben SA, Schoonhoven L, Meijs TH, van Vugt AB, van Grunsven PM. Prevalence and relief of pain in trauma patients in emergency medical services. *Clin J Pain* 2011;**27**:587–92.
10. Manou-Stathopoulou V, Korbonits M, Ackland GL. Redefining the perioperative stress response: a narrative review. *Br J Anaesth* 2019;**123**:570–83.
11. Sacco M, Meschi M, Regolisti G, Detrenis S, Bianchi L, Bertorelli M, *et al.* The relationship between blood pressure and pain. *J Clin Hypertens* 2013;**15**:600–5.
12. Ismailov RM, Ness RB, Redmond CK, Talbott EO, Weiss HB. Trauma associated with cardiac dysrhythmias: results from a large matched case-control study. *J Trauma* 2007;**62**:1186–91.
13. Roberts I, Evans P, Bunn F, Kwan I, Crowhurst E. Is the normalisation of blood pressure in bleeding trauma patients harmful? *Lancet* 2001;**357**:385–7.
14. Ahn Y, Görlinger K, Alam HB, Eikermann M. Pain-associated respiratory failure in chest trauma. *Anesthesiology* 2013;**118**:701–8.
15. Greisen J, Juhl CB, Grøfte T, Vilstrup H, Jensen TS, Schmitz O. Acute pain induces insulin resistance in humans. *Anesthesiology* 2001;**95**:578–84.
16. Chambers JA, Guly HR. The need for better prehospital analgesia. *Arch Emerg Med* 1993;**10**:187–92.

17. Ricard-Hibon A, Chollet C, Saada S, Loridant B, Marty J. A quality control program for acute pain management in out-of-hospital critical care medicine. *Ann Emerg Med* 1999;**34**:738–44.

18. Kyranou M, Puntillo K. The transition from acute to chronic pain: might intensive care unit patients be at risk? *Ann Intensive Care* 2012;**2**:36.

19. Jennings PA, Cameron P, Bernard S, Walker T, Jolley D, Fitzgerald M, Masci K. Long-term pain prevalence and health-related quality of life outcomes for patients enrolled in a ketamine versus morphine for prehospital traumatic pain randomised controlled trial. *Emerg Med J* 2014;**31**:840–3.

20. Dunwoody CJ, Krenzischek DA, Pasero C, Rathmell JP, Polomano RC. Assessment, physiological monitoring, and consequences of inadequately treated acute pain. *Pain Manag Nurs* 2008;**9**:11–21.

21. Melcer T, Walker J, Bhatnagar V, Richard E, Han P, Sechriest I, *et al*. *Glasgow Coma Scale Scores, Early Opioids, and 4-Year Psychological Outcomes Among Combat Amputees*. San Diego, CA: Naval Health Research Center; 2014.

22. Holbrook TL, Galarneau MR, Dye JL, Quinn K, Dougherty AL. Morphine use after combat injury in Iraq and post-traumatic stress disorder. *N Engl J Med* 2010;**362**:110–7.

23. Sinatra R. Causes and consequences of inadequate management of acute pain. *Pain Med* 2010;**11**:1859–71.

24. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, *et al*. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *Pain* 2019;**160**:19–27.

25. Henschke N, Kamper SJ, Maher CG. The epidemiology and economic consequences of pain. *Mayo Clin Proc* 2015;**90**:139–47. https://doi.org/10.1016/j.mayocp.2014.09.010

26. Schirmer D, Karri J, Abd-Elsayed A. Economic burden of pain. *Guide Inpatient Pain Consult* 2020:539–46.

27. Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine J* 2008;**8**:8–20. https://doi.org/10.1016/j.spinee.2007.10.005

28. Voscopoulos C, Lema M. When does acute pain become chronic? *Br J Anaesthesia* 2010;**105**:i69–85. https://doi.org/10.1093/bja/aeq323

29. McGreevy K, Bottros MM, Raja SN. Preventing chronic pain following acute pain: risk factors, preventive strategies, and their efficacy. *Eur J Pain Suppl* 2011;**5**:365–72.

30. Anekar AA, Hendrix JM, Cascella M. *WHO Analgesic Ladder*. Tampa, FL: StatPearls Publishing; 2023.

31. Gupta N, Case AA. Adjuvant Analgesics. In Smith HS, Pilitsis JG, editors. *The Art and Science of Palliative Medicine*. 1st edn. New York: AME Publishing Company; 2014. pp. 209–22.

32. Association of Ambulance Services Chief Executives (AACE) and Joint Royal Colleges Ambulance Liaison Committee (JRCALC). *JRCALC Clinical Guidelines 2021*. Bridgwater: Class Professional Publishing; 2021.

33. Hachimi-Idrissi S. Guidelines for the Management of Acute Pain in Emergency Situations. Aartselaar: European Society for Emergency Medicine; 2020.

34. Baumann L, Bello C, Georg FM, Urman RD, Luedi MM, Andereggen L. Acute pain and development of opioid use disorder: patient risk factors. *Curr Pain Headache Rep* 2023;**27**:437–44.

35. Balzer N, McLeod SL, Walsh C, Grewal K. Low-dose ketamine for acute pain control in the emergency department: a systematic review and meta-analysis. *Acad Emerg Med* 2021;**28**:444–54.

36. Cogan CJ, Kandemir U. Role of peripheral nerve block in pain control for the management of acute traumatic orthopaedic injuries in the emergency department: diagnosis-based treatment guidelines. *Injury* 2020;**51**:1422–5.

37. Beaudrie-Nunn AN, Wieruszewski ED, Woods EJ, Bellolio F, Mara KC, Canterbury EA. Efficacy of analgesic and sub-dissociative dose ketamine for acute pain in the emergency department. *Am J Emerg Med* 2023;**70**:133–9.

38. Nguyen T, Mai M, Choudhary A, Gitelman S, Drapkin J, Likourezos A, *et al*. Comparison of nebulized ketamine to intravenous subdissociative dose ketamine for treating acute painful conditions in the emergency department: a prospective, randomized, double-blind, double-dummy controlled trial. *Ann Emerg Med* 2024;**84**:354–62.

39. Esfahani H, Khazaeipour Z, Safaie A, Aghili SM. Ketamine sub-dissociative dose vs. morphine sulfate for acute pain control in patients with isolated limb injuries in the emergency department: a randomized, double-blind, clinical trial. *Bull Emerg Trauma* 2021;**9**:73–9.

40. Puzio TJ, Klugh J, Wandling MW, Green C, Balogh J, Prater SJ, *et al*. Ketamine for acute pain after trauma: the KAPT randomized controlled trial. *Trials* 2022;**23**:599.

41. Andolfatto G, Innes K, Dick W, Jenneson S, Zed PJ, Stenstrom R. Prehospital analgesia with intra-nasal ketamine: a randomized double-blind pilot study. *Can J Emerg Med* 2018;**20**:S57.

42. Tran KP, Nguyen Q, Truong XN, Le V, Le VP, Mai N, *et al*. A comparison of ketamine and morphine analgesia in prehospital trauma care: a cluster randomized clinical trial in rural Quang Tri province, Vietnam. *Prehosp Emerg Care* 2014;**18**:257–64.

43. Le Cornec C, Le Pottier M, Broch H, Tixier AM, Rousseau E, Laribi S, *et al*. Ketamine compared with morphine for out-of-hospital analgesia for patients with traumatic pain: a randomized clinical trial. *JAMA Netw* 2024;**7**:e2352844.

44. Jennings PA, Cameron P, Bernard S, Walker T, Jolley D, Fitzgerald M, Masci K. Morphine and ketamine is superior to morphine alone for out-of-hospital trauma analgesia: a randomized controlled trial. *Ann Emerg Med* 2012;**59**:497–503.

45. Johansson P, Kongstad P, Johansson A. The effect of combined treatment with morphine sulphate and low-dose ketamine in a prehospital setting. *Scand J Trauma Resusc Emerg Med* 2009;**17**:61.

46. Galinski M, Dolveck F, Combes X, Limoges V, Smaïl N, Pommier V, *et al*. Management of severe acute pain in emergency settings: ketamine reduces morphine consumption. *Am J Emerg Med* 2007;**25**:385–90.

47. Green SM, Clark R, Hostetler MA, Cohen M, Carlson D, Rothrock SG. Inadvertent ketamine overdose in children: clinical manifestations and outcome. *Ann Emerg Med* 1999;**34**:492–7.

48. Sehdev RS, Symmons DA, Kindl K. Ketamine for rapid sequence induction in patients with head injury in the emergency department. *Emerg Med Australas* 2006;**18**:37–44.

49. Sibley A, Mackenzie M, Bawden J, Anstett D, Villa-Roel C, Rowe BH. A prospective review of the use of ketamine to facilitate endotracheal intubation in the helicopter emergency medical services (HEMS) setting. *Emerg Med J* 2011;**28**:521–5. https://doi.org/10.1136/emj.2009.088237

50. Bredmose PP, Lockey DJ, Grier G, Watts B, Davies G. Pre-hospital use of ketamine for analgesia and procedural sedation. *Emerg Med J* 2009;**26**:62–4.

51. Burnett AM, Salzman JG, Griffith KR, Kroeger B, Frascone RJ. The emergency department experience with prehospital ketamine: a case series of 13 patients. *Prehosp Emerg Care* 2012;**16**:553–9. https://doi.org/10.3109/10903127.2012.695434

52. Fisher AD, Rippee B, Shehan H, Conklin C, Mabry RL. Prehospital analgesia with ketamine for combat wounds: a case series. *J Spec Oper Med* 2014;**14**:11–7.

53. McQueen C, Crombie N, Cormack S, Wheaton S. Prehospital use of ketamine for analgesia and procedural sedation by critical care paramedics in the UK: a note of caution? *Emerg Med J* 2014;**31**:1029.

54. Losvik OK, Murad MK, Skjerve E, Husum H. Ketamine for prehospital trauma analgesia in a low-resource rural trauma system: a retrospective comparative study of ketamine and opioid analgesia in a ten-year cohort in Iraq. *Scand J Trauma Resusc Emerg Med* 2015;**23**:94.

55. Hollis GJ, Keene TM, Ardlie RM, Caldicott DGE, Stapleton SG. Prehospital ketamine use by paramedics in the Australian capital territory: a 12 month retrospective analysis. *Emerg Med Australas* 2017;**29**:89–95.

56. Cowley A, Williams J, Westhead P, Gray N, Watts A, Moore F. A retrospective analysis of ketamine administration by critical care paramedics in a pre-hospital care setting. *Br Paramed J* 2018;**2**:25–31. https://doi.org/10.29045/14784726.2018.03.2.4.25

57. Lyon RF, Schwan C, Zeal J, Kharod C, Staak B, Petersen C, *et al*. Successful use of ketamine as a prehospital analgesic by pararescuemen during operation enduring freedom. *J Spec Oper Med* 2018;**18**:70–3.

58. Jabourian A, Dong F, Mackey K, Vaezazizi R, Pennington TW, Neeki M. Evaluation of safety and efficacy of prehospital paramedic administration of sub-dissociative dose of ketamine in the treatment of trauma-related pain in adult civilian population. *Cureus* 2020;**12**:e9567. https://doi.org/10.7759/cureus.9567

59. Haske D, Dorau W, Heinemann N, Eppler F, Schopp T, Schempf B. Efficacy and safety in ketamine-guided prehospital analgesia for abdominal pain. *Intern Emerg Med* 2022;**17**:2291–7. https://doi.org/10.1007/s11739-022-03091-w

60. Eimer C, Reifferscheid F, Jung P, Rudolph M, Terboven T, Hoffmann F, *et al*. Pre-hospital analgesia in pediatric trauma and critically ill patients: an analysis of a German air rescue service. *Scand J Trauma Resusc Emerg Med* 2023;**31**:5. https://doi.org/10.1186/s13049-023-01069-x

61. Frawley J, Goyal A, Gappy R, Sandoval S, Chen NW, Crowe R, Swor R. A comparison of prehospital pediatric analgesic use of ketamine and opioids. *Prehosp Emerg Care* 2023;**27**:915–9. https://doi.org/10.1080/10903127.2023.2183295

62. Tohira H, Brink D, Davids L, Brits R, Ball S, Schug S, *et al*. Use of ketamine wafer for pain management by volunteer emergency medical technicians in rural Western Australia. *Emerg Med Australas* 2023;**35**:786–91. https://doi.org/10.1111/1742-6723.14226

63. Scaggs TR, Glass DM, Hutchcraft MG, Weir WB. Prehospital ketamine is a safe and effective treatment for excited delirium in a community hospital based EMS system. *Prehosp Disaster Med* 2016;**31**:563–9.

64. Linder LM, Ross CA, Weant KA. Ketamine for the acute management of excited delirium and

agitation in the prehospital setting. *Pharmacotherapy* 2018;**38**:139–51.

65. Ho JD, Smith SW, Nystrom PC, Dawes DM, Orozco BS, Cole JB, Heegaard WG. Successful management of excited delirium syndrome with prehospital ketamine: two case examples. *Prehosp Emerg Care* 2013;**17**:274–9.
66. Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. *Am J Emerg Med* 2008;**26**:985–1028. https://doi.org/10.1016/j.ajem.2007.12.005
67. Svenson JE, Abernathy MK. Ketamine for prehospital use: new look at an old drug. *Am J Emerg Med* 2007;**25**:977–80.
68. Porter K. Ketamine in prehospital care. *Emerg Med J* 2004;**21**:351–4.
69. Cottingham R, Thomson K. Use of ketamine in prolonged entrapment. *J Accid Emerg Med* 1994;**11**:189–91.
70. Bansal A, Miller M, Ferguson I, Burns B. Ketamine as a prehospital analgesic: a systematic review. *Prehosp Disaster Med* 2020;**35**:314–21.
71. Jennings PA, Cameron P, Bernard S. Ketamine as an analgesic in the pre-hospital setting: a systematic review. *Acta Anaesthesiol Scand* 2011;**55**:638–43.
72. Sandberg M, Hyldmo PK, Kongstad P, Dahl Friesgaard K, Raatiniemi L, Larsen R, *et al*. Ketamine for the treatment of prehospital acute pain: a systematic review of benefit and harm. *BMJ Open* 2020;**10**:e038134. https://doi.org/10.1136/bmjopen-2020-038134
73. Yousefifard M, Askarian-Amiri S, Alavi SNR, Sadeghi M, Saberian P, Baratloo A, *et al*. The efficacy of ketamine administration in prehospital pain management of trauma patients; a systematic review and meta-analysis. *Arch Acad Emerg Med* 2020;**8**:e1.
74. Schulz KF, Grimes DA. Blinding in randomised trials: hiding who got what. *Lancet* 2002;**359**:696–700.
75. Goyal A, Frawley J, Gappy R, Sandoval S, Chen NW, Crowe R, Swor R. Prehospital ketamine use in pediatrics. *Prehosp Emerg Care* 2023;**27**:360–5. https://doi.org/10.1080/10903127.2022.2096161
76. National Institute for Health and Care Research. *A Randomised Controlled Trial of Paramedic Analgesia Comparing Ketamine and MorphiNe in Trauma (PACKMaN)*. NIHR; 2021. URL: https://fundingawards.nihr.ac.uk/award/NIHR128086 (accessed 12 May 2024).
77. Chang AK, Bijur PE, Napolitano A, Lupow J, Gallagher EJ. Two milligrams iv hydromorphone is efficacious for treating pain but is associated with oxygen desaturation. *J Opioid Manag* 2009;**5**:75–80.
78. Droney JM, Gretton SK, Sato H, Ross JR, Branford R, Welsh KI, *et al*. Analgesia and central side-effects: two separate dimensions of morphine response. *Br J Clin Pharmacol* 2013;**75**:1340–50. https://doi.org/10.1111/bcp.12008
79. Wong JY, Carvalho B, Riley ET. Intrathecal morphine 100 and 200 mug for post-cesarean delivery analgesia: a trade-off between analgesic efficacy and side effects. *Int J Obstet Anesth* 2013;**22**:36–41. https://doi.org/10.1016/j.ijoa.2012.09.006
80. Zhou K, Sheng S, Wang GG. Management of patients with pain and severe side effects while on intrathecal morphine therapy: a case study. *Scand J Pain* 2017;**17**:37–40. https://doi.org/10.1016/j.sjpain.2017.07.006
81. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. *Ann Emerg Med* 2011;**57**:449–61. https://doi.org/10.1016/j.annemergmed.2010.11.030
82. Stubhaug A, Breivik H, Eide P, Kreunen M, Foss A. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. *Acta Anaesthesiol Scand* 1997;**41**:1124–32.
83. McNicol ED, Schumann R, Haroutounian S. A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. *Acta Anaesthesiol Scand* 2014;**58**:1199–213. https://doi.org/10.1111/aas.12377
84. Dailey MW, Goldfine C, Tran S. EMS analgesia practices in the United States: changes in practice over the last 5 years. *Acad Emerg Med* 2014;**1**:S74–S5.
85. Haske D, Schempf B, Gaier G, Niederberger C. Prehospital analgesia performed by paramedics: quality in processes and effects under medical supervision. [German]. *Anaesthesist* 2014;**63**:209–16.
86. Buckland DM, Crowe RP, Cash RE, Gondek S, Maluso P, Sirajuddin S, *et al*. Ketamine in the prehospital environment: a national survey of paramedics in the United States. *Prehosp Disaster Med* 2018;**33**:23–8.
87. von Vopelius-Feldt J, Benger J. Who does what in prehospital critical care? An analysis of competencies of paramedics, critical care paramedics and prehospital physicians. *Emerg Med J* 2013;**31**:1009–13.
88. Michelet F, Smyth M, Lall R, Noordali H, Starr K, Berridge L, *et al*. Randomised controlled trial of analgesia for the management of acute severe pain from traumatic injury: study protocol for the paramedic analgesia comparing ketamine and morphine in trauma (PACKMaN). *Scand J Trauma Resusc Emerg Med* 2023;**31**:84.

89. Cooper SA, Desjardins PJ, Turk DC, Dworkin RH, Katz NP, Kehlet H, *et al*. Research design considerations for single-dose analgesic clinical trials in acute pain: IMMPACT recommendations. *Pain* 2016;**157**:288–301. https://doi.org/10.1097/j.pain.0000000000000375

90. Farrar JT, Berlin JA, Strom BL. Clinically important changes in acute pain outcome measures: a validation study. *J Pain Symptom Manage* 2003;**25**:406–11. https://doi.org/10.1016/S0885-3924(03)00162-3

91. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, *et al*. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Res* 2011;**20**:1727–36.

92. Jumbo SU, MacDermid JC, Kalu ME, Packham TL, Athwal GS, Faber KJ. Measurement properties of the Brief Pain Inventory-Short Form (BPI-SF) and Revised Short Mcgill Pain Questionnaire version-2 (SF-MPQ-2) in pain-related musculoskeletal conditions: a systematic review. *Clin J Pain* 2021;**37**:454–74.

93. Nicholas M, Vlaeyen JW, Rief W, Barke A, Aziz Q, Benoliel R, *et al*.; The IASP Taskforce for the Classification of Chronic Pain. The IASP classification of chronic pain for ICD-11: chronic primary pain. *Pain* 2019;**160**:28–37.

94. Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, *et al*. Chronic pain as a symptom or a disease: the IASP Classification of Chronic Pain for the International Classification of Diseases (ICD-11). *Pain* 2019;**160**:19–27. https://doi.org/10.1097/j.pain.0000000000001384

95. National Clinical Guideline Centre. *Major Trauma: Assessment and Initial Management*. 2016. URL: www.nice.org.uk/guidance/ng39/evidence/full-guideline-2308122833 (accessed 10 September 2025).

96. Riccardi A, Guarino M, Serra S, Spampinato MD, Vanni S, Shiffer D, *et al*.; Study and Research Center of the Italian Society of Emergency Medicine. Narrative review: low-dose ketamine for pain management. *J Clin Med* 2023;**12**:3256.

97. Health Research Authority. *MHRA and HRA Position on Who Can Act as a Chief Investigator*. Health Research Authority; 2020. URL: www.hra.nhs.uk/planning-and-improving-research/research-planning/roles-and-responsibilities/mhra-and-hra-position-who-can-act-chief-investigator/ (accessed 15 August 2024).

98. Wankhade P, Cook IG, Halsall JP. Ethnic minorities and their health needs: crisis of perception and behaviours. *Illn Crisis Loss* 2014;**22**:145–58. https://doi.org/10.2190/IL.22.2.e

99. Goddard M, Smith P. Equity of access to health care services: theory and evidence from the UK. *Soc Sci Med* 2001;**53**:1149–62. https://doi.org/10.1016/S0277-9536(00)00415-9

100. Campbell CM, Edwards RR. Ethnic differences in pain and pain management. *Pain Manag* 2012;**2**:219–30.

101. Hewes HA, Dai M, Mann NC, Baca T, Taillac P. Prehospital pain management: disparity by age and race. *Prehosp Emerg Care* 2018;**22**:189–97.

102. Robertson R, Williams E, Buck D, Breckwoldt J. *Ethnic Health Inequalities and the NHS*. London: The King's Fund and NHS Race and Health Observatory; 2021. pp. 1613–4.

103. Todkill D, Loveridge P, Elliot AJ, Morbey RA, Edeghere O, Rayment-Bishop T, *et al*. Utility of ambulance data for real-time syndromic surveillance: a pilot in the West Midlands region, United Kingdom. *Prehosp Disaster Med* 2017;**32**:667–72.

104. Baker DW, Hasnain-Wynia R, Kandula NR, Thompson JA, Brown ER. Attitudes toward health care providers, collecting information about patients' race, ethnicity, and language. *Med Care* 2007;**45**:1034–42.

105. Bell F, Crabtree R, Wilson C, Miller E, Byrne R. Ambulance service recognition of health inequalities and activities for reduction: an evidence and gap map of the published literature. *Br Paramed J* 2024;**9**:47–57.

106. Vijayananthan A, Nawawi O. The importance of Good Clinical Practice guidelines and its role in clinical trials. *Biomed Imaging Interv J* 2008;**4**:e5.

107. House of Lords Merits of Statutory Instruments Committee. *Medicines for Human Use (Clinical Trials) Regulations 2004: 4th Report of Session 2003-04*. London: Stationery Office; 2004.

108. Bone MF. Ethics of research in clinical emergencies: UK regulation inconsistent with European Law. *Res Ethics* 2007;**3**:97–100. https://doi.org/10.1177/174701610700300310

109. Hutchison M, Comper P, Mainwaring L, Richards D. The influence of musculoskeletal injury on cognition: implications for concussion research. *Am J Sports Med* 2011;**39**:2331–7.

110. Moriarty O, McGuire BE, Finn DP. The effect of pain on cognitive function: a review of clinical and preclinical research. *Prog Neurobiol* 2011;**93**:385–404.

111. Solberg Nes L, Roach AR, Segerstrom SC. Executive functions, self-regulation, and chronic pain: a review. *Ann Behav Med* 2009;**37**:173–83.

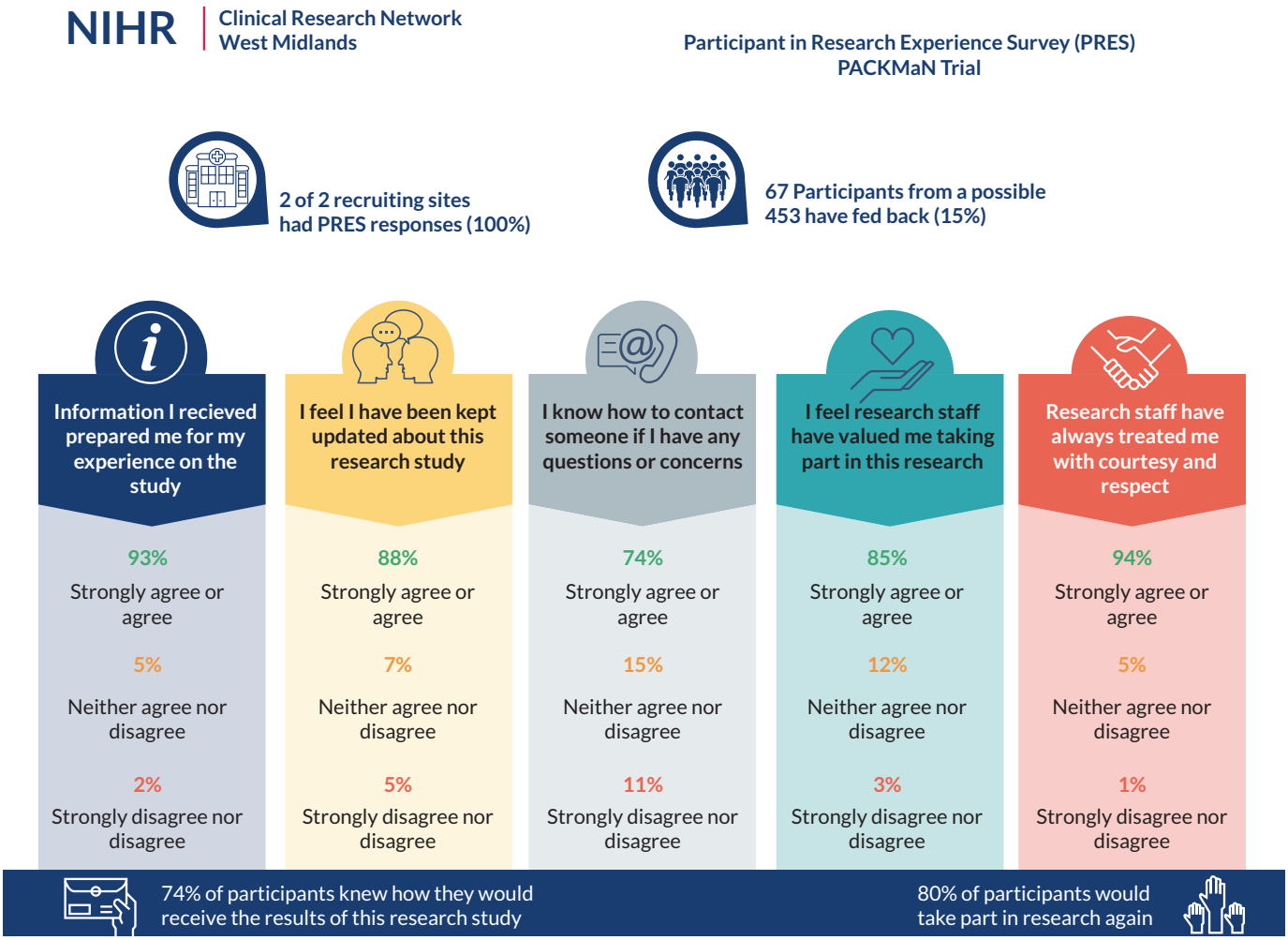
112. Aja B. The effects of pain on informed consent. *Nurse Anesthesia Student Capstones* 2017;**10**.

113. French SC, Salama NP, Baqai S, Raslavicus S, Ramaker J, Chan SB. Effects of an educational intervention on prehospital pain management. *Prehosp Emerg Care* 2006;**10**:71–6.

Appendix 1 Brief patient information statement read by paramedics prior to enrolling a patient

I would like to give you something to relieve your pain by injecting a strong pain killer into one of your veins. The Ambulance service is participating in a clinical trial comparing two different pain killing drugs to understand which works best in ambulance services. I am planning on giving you the trial medication. This will mean you receive either morphine or ketamine, but we will not know which you receive. However, you do not have to participate in the trial. If you prefer, I can provide our usual treatment morphine instead. Is it OK for me to give you the trial medication?

Appendix 2 Participant in research experience survey



This synopsis should be referenced as follows:
Smyth MA, Noordali H, Lall R, Michelet F, Petrou S, Khan K, *et al.* Paramedic analgesia comparing ketamine and morphine in trauma. A synopsis of the PACKMaN double-blind RCT. *Health Technol Assess* 2026;**30**(57). https://doi.org/10.3310/KGTO6391

CPMS ID	46938	PACKMaN

	Participants	Sites
Recruited	453	2
PRES responses	67	2
	15%	100%

	Number of respondents who ticked each option				
	Strongly Agree (5)	Agree (4)	Neither agree nor disagree (3)	Disagree (2)	Strongly disagree (1)
The information that I received before taking part prepared me for my experience on the study	30	27	3	0	1
I feel I have been kept updated about this research study	28	25	4	1	2
I know how to contact someone from the research team if I have any questions or concerns	16	32	10	5	2
I feel research staff have valued my taking part in this research study	30	25	8	1	1
Research staff have always treated me with courtesy and respect	38	23	3	0	1
I would consider taking part in research again	32	20	9	1	3

	Yes	Yes, to some extent	No
I know how I will receive the results of this research study	17	30	17

Analysis			
'Minimalist' bar charts showing breakdown of responses to each question	Strongly agree or Agree	Neutral	Disagree or Strongly disagree
	93%	5%	2%
	88%	7%	5%
	74%	15%	11%
	85%	12%	3%
	94%	5%	2%
	80%	14%	6%

	Yes	Yes, to some extent	No
	27%	47%	27%