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Cost-effectiveness of paramedic administered ketamine compared to morphine for the management of acute severe pain from traumatic injury

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Title page

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Cost-effectiveness of paramedic administered ketamine compared to morphine for the management of acute severe pain from traumatic injury.

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Abstract

Background

Pain after traumatic injury is common, yet few patients receive adequate pain relief. NHS paramedics have a limited formulary to treat severe pain.

Objectives

To estimate the cost-effectiveness of ketamine versus morphine for severe pain in acute traumatic injury.

Methods

A cost-utility analysis was conducted based on data from a pragmatic, multicentre, randomised controlled trial (PACKMAN). The base-case analysis took the form of an intention-to-treat analysis conducted from a UK National Health Service (NHS) and personal social services (PSS) perspective and separately from a societal perspective. Costs (£ 2021–2022 prices) were collected prospectively over a 6-month follow-up period. A bivariate regression of costs and quality-adjusted life-years (QALYs), with multiple imputation of missing data, was conducted to estimate the incremental cost per QALY gained and the incremental net monetary benefit (INMB) of ketamine in comparison to morphine. Sensitivity and pre-specified subgroup analyses explored uncertainty and heterogeneity in cost-effectiveness estimates.

Results

Participants (n=416) were randomised to ketamine (n=206) or morphine (n=210) amongst whom complete data for the economic evaluation was available for 189 (45.4%) participants. Mean (standard deviation [SD]) observed NHS and PSS costs over 6 months were £5,191 (£3,155) in the ketamine arm versus £5,143 (£3,897) in the morphine arm (mean difference [MD]: £47). Mean

(SD) observed QALY estimates were 0.309 (0.10) versus 0.293 (0.010), respectively (MD: 0.016).

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. 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 lower 54%-62% probability of cost-effectiveness. The base-case cost-effectiveness results remained robust to other sensitivity analyses.

Conclusions

This economic evaluation found that ketamine administered by paramedics to adults with severe pain following traumatic injuries is cost-effective compared to morphine. However, our results are subject to high levels of missing data, which were handled through recommended multiple imputation techniques.

Keywords

Economic costs, Health-related quality of life, Cost-effectiveness, ketamine, morphine, severe pain, acute traumatic injury

Background

It has been reported that trauma accounts for 24% of UK ambulances service workload (1).. At least 70% of ambulance calls involve patients experiencing pain (2). NHS paramedics have a limited formulary to treat severe pain (2). Observational studies suggest that current treatments leave many patients with inadequate pain relief in the prehospital environment (3-7). In 2004, the World Health Organisation declared that effective management of pain is a universal human right (8). Poorly managed acute pain is also associated with increased chronic pain. Studies indicate chronic pain is common following trauma with a reported incidence of 15-30%, increasing to 62% in patients suffering major trauma (9-11). Poorly managed postoperative pain leads to persistent pain in 10-50% of common surgeries, and that pain is severe in about 2-10% of these patients (12). Military personnel injured in recent conflicts demonstrate a link between acute pain management and depression and post-traumatic stress disorder (PTSD). Early aggressive pain management exerts a protective effect on the development of PTSD (odds ratio (OR) 0.47 (95%CI 0.34-0.66) and depression (0.40 (95%CI 0.17 – 0.94).(13, 14) Provision of early and effective analgesia has the potential to reduce the risk of developing chronic pain and adverse mental health outcomes post trauma, which may in turn impact on patient’s long term quality of life (15, 16).

A barrier to effective pain treatment is the limited formulary available to paramedics. The most frequently used drug for moderate to severe pain outside a hospital is morphine (17). Yet morphine has several side effects (nausea, confusion, dizziness, drowsiness, respiratory depression, arrhythmia) that may limit its use (18-21). This, and concerns about the risk of persistent opioid use following initial exposure, limits effective use by clinicians (22). Ketamine is perceived by many to be an ideal prehospital analgesic agent, favoured for its rapid onset of action, effective analgesia, good haemodynamic stability, and preservation of upper airway reflexes (23). Ketamine has a distinct dose-response gradient in which smaller doses (0.1-0.3 mg/kg) are analgesic and larger doses (2 mg/kg) have an anaesthetic effect (24). It exerts its effect by “disconnecting” the thalamocortical and limbic systems, effectively dissociating the central nervous system (CNS) from outside stimuli (e.g. pain, sight, sound) (25). Ketamine also stimulates the sympathetic nervous system and moderately increases heart rate and blood pressure. Ketamine does not affect respiration; patients breathe spontaneously and maintain airway control (26). Furthermore, there is evidence to indicate that perioperative ketamine analgesia may prevent hyperalgesia, reducing the risk of developing persistent post-operative pain (27, 28). This suggests the potential for ketamine analgesia to be associated with a lower incidence of chronic pain post trauma.

Ketamine has been advocated as an ideal prehospital analgesic due to its favourable pharmacokinetics (29). In the UK, ketamine is currently restricted for use by prehospital doctors and a limited pool of specialist critical care paramedics (CCPs), targeted at the small number of cases needing critical care support (30, 31). The lack of evidence and UK experience with ketamine limits access to a potentially effective treatment. Most trials of ketamine for analgesia have been small, of insufficient quality and were conducted in North America or Australia (32-36). Patient expectations and approaches to health service delivery in these countries differ from the UK. No studies addressing the cost-effectiveness of ketamine for analgesia have been published. The National Institute for Health and Care Excellence (NICE) in the UK has identified the need for a pragmatic, randomised trial to determine the clinical and cost-effectiveness of ketamine against standard care (morphine)(37). This study therefore aimed to estimate the cost-effectiveness of ketamine for severe pain in acute traumatic injury when delivered by UK paramedics. The findings are intended to inform policy makers, guideline developers and ambulance services as to whether ketamine should be added to the paramedic formulary.

Methods

Trial background

The Paramedic Analgesia Comparing Ketamine and MorphiNe (PACKMAN) Trial was a pragmatic, multicentre, randomised, double blind randomised controlled trial (RCT) comparing the clinical and cost-effectiveness of ketamine versus morphine for severe pain in acute traumatic injury: the protocol has been published previously (38). In brief, acute trauma patients, aged 16 and over, who reported a pain score ≥7/10 on a 0-10 numeric rating scale (NRS) following acute traumatic injury, with Intravenous (IV) or intraosseous (IO) access, determined by a paramedic to require IV morphine or equivalent were eligible. The trial had a prespecified target sample size of 446 participants (38). Recruitment occurred between 10th November 2021 and 16th May 2023 from two large NHS ambulance services (West Midlands and Yorkshire NHS Ambulance Services) in England. The treatment intervention, ketamine, was supplied in ampoules containing 15 mg in 1 ml. The control intervention, morphine, was supplied in ampoules containing 10 mg in 1 ml. The trial drugs were administered by slow IV (or IO) injection, titrated to effect over five minutes, aiming to give the minimal effective dose. If the patient continued to report pain 5 minutes after receiving the first full syringe (10 ml), a second syringe was prepared and administered in a similar manner by the attending paramedic. A maximum of 20 ml of trial drug could be administered, equating to a maximum dose of either 20 mg morphine or 30 mg ketamine. The ampoules were labelled as trial related investigational medicinal product (IMP) and paramedics were not able to identify which treatment they were administering (38). Participants were randomised (1:1 ratio) to either ketamine or morphine. Numbered study drug packs in a pre-randomised sequence, were carried by participating ambulance paramedics. Randomisation occurred when the trial IMP pack was opened. The primary clinical outcome was the Sum of Pain Intensity Difference (SPID) assessed using a 0-10 numeric rating scale. Pain intensity was recorded prior to treatment administration and then at regular intervals following randomisation until arrival at hospital. Other important outcomes included overall pain relief, patient experience, tolerability, and the economic outcomes described below.

Overview of economic analyses

The cost-utility analysis involved evaluation of economic costs, health-related quality of life (HRQoL) outcomes and cost-effectiveness of ketamine versus morphine where cost-effectiveness was expressed in terms of incremental cost per quality adjusted life year (QALY) gained. The base-case economic evaluation took the form of an intention-to-treat, imputed analysis conducted from a UK National Health Service (NHS) and personal social services (PSS) perspective in line with the NICE reference case (39). The NHS payer perspective considers intervention-related treatment costs and other health service resource use and costs whilst a personal social services perspective includes services provided by local authorities for vulnerable groups, including older people. A six-month time horizon was used for the economic evaluation, consistent with the duration of trial follow-up. Three months is typically regarded as the threshold for chronic pain, and extending follow-up to six months allowed observation of whether early effects persist into the chronic phase. No discounting was required due to the time horizon adopted.

Costs

Three broad resource use and costs categories were delineated for cost estimation: (i) Direct intervention costs (medication costs); (ii) Direct healthcare and PSS (e.g. medications for side-effects, outpatient appointments, community health and social care) use during the 6 month follow-up; and (iii) for the purposes of a sensitivity analysis conducted from a societal perspective also included non-NHS & PSS costs (e.g. value of lost productivity, out of pocket expenses). All costs were expressed in pounds sterling and valued in 2021–22 prices. Where required, costs were inflated or deflated to 2021–22 prices using the NHS Cost Inflation Index (NHSCII)(40). The PACKMaN trial focused on administration of two alternative medications for pain relief in patients with severe pain. The intervention arm received ketamine hydrochloride whilst the control arm received morphine sulphate. The intervention components, how they were collected, associated resource use and source of unit costs are summarised in Supplementary Table 1 (Appendix). In accordance with NICE guidance, we captured NHS and PSS costs for both arms of the trial (39). This included within-ambulance costs, inpatient care, outpatient care, community care, accident and emergency admission, medication, and personal social services. The methods for capturing the resource use and the sources for unit costs are outlined in Supplementary Table 2 (Appendix). Within ambulance costs were captured through the ambulance service data form, index admission costs were collected via the hospital data collection form, whilst the remaining health and social service resource use was collected through participant-completed questionnaires completed at 3 and 6 months post-randomisation. The identified resource inputs were valued using unit costs (Supplementary Table 3) identified through national cost compendia in accordance with NICE's Guide to the Methods of Technology Appraisal (39). Unit cost data were derived based on NHS England's National schedule of NHS costs 2021-22 schedules (41), the Personal social services research unit (PSSRU) Unit Costs of Health and Social Care 2022 compendium (40), 2021-22 volumes of the British National Formulary (42), NHS Supply Chain Catalogue 2021-22 (43), and the 2021-22 National Health Service Business Service Authority (NHSBSA) Prescription Cost Analysis (PCA) schedule (44). Analyses from a societal perspective additionally encompassed economic values for work absences (by patients and their caregivers), travel costs and privately incurred health expenditures. Cost information was self-reported by trial participants.

Health-related quality of life outcomes

HRQoL were assessed using the EQ-5D-5L instrument, which defines HRQoL in terms of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each with five levels of severity(45). The EQ-5D-5L was chosen because it provides improved descriptive sensitivity, greater discriminatory power, and reduced ceiling effects compared with the EQ-5D-3L, particularly in populations with mobility and pain problems such as trauma and musculoskeletal patients (46-48). For ethical, logistical and pragmatic reasons, it was not possible to capture baseline EQ-5D-5L measurements in patients suffering acute pain following trauma within this trial. This is not uncommon within trials involving emergency and critical care settings (49). Ideally, the EQ-

5D-5L would be completed at the time of randomisation or as soon as possible afterwards. This however was not possible in this trial. National age and gender specific norms for EQ-5D utility values were therefore applied at baseline (50). These normative values, derived from a large, nationally representative sample of the English population, were estimated using EQ-5D responses collected through the Health Survey for England and weighted to reflect the demographic structure of the population. Utilities were calculated for each age–gender stratum using the recommended UK EQ-5D value set, and participants in this trial were assigned the normative utility corresponding to their age group and gender at randomisation. HRQoL at 3 and 6 months post-randomisation was assessed using patient-completed EQ-5D-5L responses. Responses to the EQ-5D-5L descriptive system were mapped onto the EQ-5D-3L value set using the Alava HM et al. interim cross-walk algorithm (51), as recommended by NICE in England and Wales (39). Empirical analyses show that cross-walked EQ-5D-5L utilities have a compressed distribution with lower variance and slightly lower mean values compared with native 3L or 5L utilities (52). This redistribution can reduce sensitivity to small changes in health, leading to slightly more conservative QALY estimates (53). Patient-level QALYs were estimated using the area under the curve approach, assuming linear interpolation between the utility scores, i.e., the preference-based values attached to the health states generated from the EQ-5D-5L descriptive system.

Handling of missing data

Multiple imputation by chained equations was used to predict missing costs and health utility scores based on the assumption that data were missing at random (MAR). To examine the plausibility of the MAR assumption, we conducted a series of logistic regression analyses comparing baseline demographic, clinical, and trial process variables between participants with and without missing EQ-5D and cost data at follow-up. Several variables including baseline EQ-5D, age, and ambulance service were found to be associated with missingness and were therefore included in the imputation model to strengthen the plausibility of the MAR assumption. Imputation was achieved using predictive mean matching, which has the advantage of preserving nonlinear relationships and correlations between variables within the data. Fifty imputed datasets were generated to inform the base-case and subsequent sensitivity and subgroup analyses. Parameter estimates were pooled across the imputed datasets using Rubin's rules to account for between- and within-imputation components of variance terms associated with parameter estimates (54).

Cost-effectiveness analysis

Mean resource use, cost and health utility values were compared between the trial arms using two sample t-tests. Mean incremental costs and mean incremental QALYs were estimated using seemingly unrelated regression (SUR) methods that account for the correlation between costs and outcomes (55). Differences between groups, along with confidence intervals (CIs), were estimated using non-parametric bootstrap estimates (10,000 replications) of regression models. The cost equation was adjusted using: type of ambulance service (West Midland Ambulance Service (WMAS), Yorkshire Ambulance Service (YAS)), age category (<60, ≥60), gender (male, female), administration of IV analgesia prior to randomisation (Yes, No), and weight ((i) >0 and <70, ii) ≥70 and <85, iii) ≥85 kg). The QALY equation was adjusted using baseline utilities, ambulance service (WMAS, YAS), age category (<60, ≥60), gender (male, female), administration of IV analgesia prior to randomisation (Yes, No), and weight ((i) >0 and <70, ii) ≥70 and <85, iii) ≥85 kg)). Following imputation, bootstrapping was used to generate the joint distribution of costs and outcomes and to populate a cost-effectiveness plane. The incremental cost-effectiveness ratio (ICER) for ketamine was estimated by dividing the between-group difference in adjusted mean total costs by the between-group difference in adjusted mean QALYs. Mean ICER values were compared against cost-effectiveness threshold values (i.e. society’s willingness to pay for an additional QALY) ranging between £20,000 and £30,000 per QALY gained in line with NICE guidance (39). ICER values lower than the threshold are considered cost-effective for use in the UK NHS. The incremental net monetary benefit (INMB) of switching from morphine to ketamine was also calculated at each of these cost-effectiveness threshold values. The net monetary benefit is the economic benefit of an intervention (expressed in monetary terms) net of all costs. A positive incremental NMB suggests that, on average, ketamine is cost-effective compared with morphine, at the given cost-effectiveness threshold.

Sensitivity and subgroup analyses

Pre-specified sensitivity analyses were undertaken to assess the impact of uncertainty surrounding components of the economic evaluation and included restricting the analyses to complete cases (i.e. the sample of participants with no missing costs or outcome data at any time point), replicating the analysis from a societal perspective, and changing the baseline utility assumption (assumed a fixed utility of 0 for everyone). Prespecified subgroup analyses were conducted by age category (<60, ≥60), gender (male, female), administration of IV analgesia prior to randomisation ((Yes, No), weight (i) >0 and <70, ii) ≥70 and

<85, iii) ≥85 kg). Interaction terms between treatment and each subgroup variable were included in the regression models to formally test whether the effect of ketamine on costs and QALYs differed across subgroups. In addition, a scenario analysis was conducted estimating the incremental cost per score point reduction in the sum of pain intensity difference (SPID) the time horizon for this was constrained to the period between randomisation and initial hospital discharge.

Results

Study population and data completeness.

Baseline characteristics of participants were well-matched between the randomised groups (Table 1). Complete QALY profiles were available for 196 (47%) participants based on the EQ-5D-5L (Table 2). Completion of resource use data for the economic evaluation was similar (53%-57%) at each time-point between the ketamine and morphine groups (Table 2). There were no differences in the sociodemographic characteristics between participants with or without complete data (Supplementary Table 4).

Cost of intervention

Mean total intervention costs are presented for each group (Supplementary Table 5). These varied between £21.76 (ketamine) and £23.89 (morphine). The information on cost components can be found in Supplementary Table 3.

Resource utilisation

For health and personal social service use, shown in Supplementary Table 5, there were no differences between the two groups in utilisation of hospital inpatient and outpatient care. In terms of community-based health and social care, there were higher visits to the GP for the ketamine arm (mean (SD) 2.45 (1.79)) vs the morphine arm (mean (SD) 1.50 (0.79)). For all other categories of community-based health and social care, there were no differences between the two groups in resource utilisation.

Total economic costs

For the base-case (imputed) analysis, mean NHS and PSS costs, inclusive of intervention costs, over the entire follow-up period were £5207 for the ketamine arm versus £5324 for the morphine arm (Supplementary Table 6). There was an incremental cost saving in the ketamine arm of £117. Mean total societal costs, for the entire follow-up period, inclusive of the intervention cost, were £6266 in the ketamine arm compared with £6373 in the morphine group (Supplementary Table 6). This generated sn incremental cost increase of £107 in favour of the ketamine arm. The estimates of economic costs for non-imputed (complete) cases are shown in Supplementary Table 5 and follow the same pattern as the imputed base case analysis.

Health-related quality of life outcomes

For the base-case analysis, mean (SE) participant reported QALY estimates for the entire period were 0.314 (0.01) for the ketamine arm versus 0.289 (0.01) for the morphine arm; the mean between group difference was 0.0253 (Supplementary Table 6).

Cost-effectiveness results: base-case analysis (imputed costs and adjusted

The base-case economic evaluation (NHS and PSS perspective, imputed costs and QALYs and adjusted for covariates) indicated that ketamine was associated with lower NHS and PSS costs (-£117, 95% CI − £849 to £597) and an improvement in QALYs (0.025, 95% CI 0.010 to 0.041). Ketamine was associated with a lower cost and an improvement in health outcomes compared to morphine, and is therefore considered dominant.. The associated mean INMB at cost-effectiveness thresholds of £20,000 and £30,000 per QALY were £631 and £884, respectively (Table 3). The base-case mean INMB was>0, suggesting that the use of ketamine would result in an average net economic gain. The probability of cost-effectiveness for ketamine was estimated as 92% and 96% at cost-effectiveness thresholds of £20,000 and £30,000 per QALY, respectively. The joint distribution of costs and outcomes for the base-case analysis is presented graphically in Fig. 1, with axes labelled for incremental costs and incremental QALYs and the four quadrants of the cost-effectiveness plane labelled to aid interpretation. The figure displays the results of 5,000 bootstrap simulations, with two reference lines representing willingness-to-pay thresholds of £20,000 and £30,000 per QALY. A higher proportion of bootstrap simulations falling below these threshold lines indicates a greater probability that ketamine is cost-effective. The cost-effectiveness acceptability curve is shown in Fig. 2, with a horizontal reference line at 50% probability to aid interpretation. Points above this line indicate that the intervention is more likely than not to be cost-effective at the corresponding willingness-to-pay threshold, whereas points below indicate a lower probability. For ketamine, the curve remains above the

50% line across commonly cited cost-effectiveness thresholds, indicating a higher likelihood than not that the intervention is cost-effective.

Sensitivity and subgroup analyses

The sensitivity analysis conducted from a societal perspective found a similar probability that ketamine was cost-effective of between 86 and 92% across cost-effectiveness thresholds (Table 3). The sensitivity analysis based on complete cases showed that there was no difference in costs and QALYs and the probability that ketamine was cost-effective decreased to between 54 and 62% across cost-effectiveness thresholds. Using a baseline utility of 0 for all participants did not impact the results.

The pre-planned subgroup analyses suggested that ketamine was more cost-effective in the following subgroups: participants aged ≥60, males, and participants that did not receive IV analgesia prior to randomisation (Table 3). However, the interaction terms in the underlying regression models were not statistically significant, indicating that differences in cost-effectiveness across these subgroups should be interpreted cautiously. The scenario analysis estimating the cost per unit change in SPID score indicated that ketamine was associated with an increase in costs from randomisation to initial discharge from hospital (£436, 95% CI − £100 to £973) and a reduction in total pain (0.0979, 95% CI -0.444 to 0.640). The mean ICER for ketamine was estimated at £4,195 (northeast quadrant) per unit pain score reduction, i.e. on average, ketamine was associated with a higher cost and a reduction in pain score.

Discussion

This trial-based economic evaluation revealed that the use of ketamine led, on average, to a modest increase in health-related quality of life, without increased cost, over a 6-month follow-up period. The resulting ICER from an NHSS and PSS perspective falls favourably below the recommended NICE cost-effectiveness threshold of £20,000 per QALY though the uncertainty around the mean ICER was large. From a societal perspective, ketamine was similarly cost-effective. There was no difference in clinical effectiveness (pain relief) when compared to morphine from randomisation to arrival at hospital.

There were some challenges when analysing the trial data, including persistent missingness at both follow up points, an imbalance of missingness by ambulance service, and a bimodal pattern of costs in both treatment arms. Given that over half of EQ-5D observations were missing at 6 months, the plausibility of the MAR assumption warranted particular consideration.. Although MAR cannot be empirically verified, the robustness of the imputation was explored by varying the imputation seed and number of (discarded) burn-ins: the results were stable. Burn in traces were checked for adequate mixing and adequacy of the Markov chain Monte Carlo (MCMC) process. The number of draws used for the imputation was 50, this was adequate when checked against the uppermost fraction of missing information (FMI), which was 40%. There is no formal way of checking if the data are missing not-at-random (MNAR), but variables were identified that predicted missingness and included in the imputation model. This approach helps satisfy the conditions under which MAR is more credible. A seemingly unrelated regression model was used for the base case analysis as it features the natural scale of the data and assumes normality of the bootstrap estimates for sample means. The distribution family for the dependent variables was explored and a gamma distribution with log link was found to improve the cost model specification, while the gaussian distribution was retained for the QALY variable. To preserve a bivariate analysis, a version of the base case was run using generalized structural equation modelling (GSEM) producing statistically similar findings. Several covariates in the base case model were significant. These were explored to see if they interacted with treatment where a significant interaction would suggest varying cost-effectiveness for the interaction sub-groups. The consistency of findings across sensitivity analyses provides some reassurance that departures from MAR, if present are unlikely to have materially influenced the conclusions. However, the possibility of missing-not-at-random (MNAR) mechanisms cannot be ruled out entirely and represents a limitation of the analysis.

Our imputed analyses of cost-effectiveness outcomes gave a more optimistic estimate, reflecting some adjustment for the patterns of missingness. The evidence of HRQoL benefits adds to the emerging evidence base from clinical trials that demonstrate improvements in pain from ketamine. (32-36) Without economic modelling beyond the current parameters of the trial, the longer-term cost-effectiveness of ketamine cannot be ascertained.

Although ketamine appeared less cost-effective in participants who were younger, required analgesia prior to randomisation, or were female, none of the interaction terms reached statistical significance. As with all sub-group analyses, these should be considered exploratory only, and our primary estimates account for all people. We used a pragmatic approach to sampling, and hence our findings should be generalisable. To the best of our knowledge there is no comparable evidence for cost-effectiveness of ketamine in trauma patients in the broader literature.

Strengths of the current economic evaluation are that the trial was prospectively designed for a cost-effectiveness analysis using individual-level data to reach a confirmatory conclusion. There are some limitations to this economic evaluation. Firstly, utility measurements were collected at only two time-points (3 months and 6 months) post-randomisation. Evidence suggests that the timing of assessment can significantly influence cost-effectiveness results when using the EQ-5D, particularly when participants experience recurrent health fluctuations (56). In such cases, the linear interpolation of utility data may fail to reflect HRQoL fluctuations over short periods and the uncertainty is compounded by missing data. While the trial may have captured differences in chronic pain, it may have missed changes in acute pain occurring before the three-month follow-up. Secondly, resource use data were retrospectively recalled by participants, and this could have led to recall bias, though we cannot predict the direction of this bias. Findings form literature are mixed, suggesting that resource use may be under-reported, over-reported or they may be good agreement between patient/carer recall and data extracted from medical records, depending on how well the resource use measures are structured (57). Because the recall periods and questionnaires were standardised across randomised groups, retrospective recall is unlikely to have biased results in favour of one group. Thirdly, our approaches to collecting resource use data did not disentangle resource use associated with trauma from resource use associated with broader health factors. Fourthly, there were high levels of missingness in the study data. However, we handled missingness within the health economic data through recommended multiple imputation techniques that address the inherent biases associated with estimating effects on the basis of complete data.

Conclusions

In this economic evaluation based upon a randomised controlled trial, ketamine administered by paramedics to adults with severe pain following traumatic injuries was cost-effective compared to morphine.

List of abbreviations

CCPs	Critical care paramedics
CI	Confidence intervals
CNS	Central nervous system
FMI	Fraction of missing information
GSEM	Generalized structural equation modelling
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IMP	Investigational medicinal product
INMB	Incremental net monetary benefit
IO	Intraosseous
IV	Intravenous
MAR	Missing at random
MCMC	Markov chain Monte Carlo
MD	Mean difference
MNAR	Missing not-at-random
NHS	National health service
NHSBSA	National Health Service Business Service Authority
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NRS	Numeric rating scale
OR	Odd ratio
PACKMAN	Paramedic Analgesia Comparing Ketamine and MorphiNe
PCA	Prescription Cost Analysis
PSS	Personal social services
PSSRU	Personal social services research unit
PTSD	Post-traumatic stress disorder
QALY	Quality-adjusted life-year
RCT	Randomised controlled trial
SD	Standard deviation
SPID	Sum of Pain Intensity Difference
SUR	Seemingly unrelated regression
WMAS	West midland ambulance service
YAS	Yorkshire ambulance service

Declarations

Ethics approval and consent to participate

Ethics approval for the PACKMAN trial was granted by the West of Scotland Research Ethics Committee (REC number 16/LO/0349) on 01/09/2020. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Patients were screened by attending paramedics, and verbal assent to participation was obtained prior to randomisation. Written informed consent was subsequently obtained by trained research paramedics, either during the patient's hospital stay or following discharge from hospital.

Trial registration

The trial was registered with the International Standard Randomised Controlled Trial Number (ISRCTN) registry (ISRCTN14124474) on 22 October 2020.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analysed during the current study are available from the corresponding author upon reasonable request.

Competing interests

None

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Author contributions

CRediT author statement

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The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care

Table 1: Baseline characteristics by trial arm

	Ketamine (n=206)	Morphine (n=210)
Baseline characteristics		
Ambulance service (n, %)		
WMAS	107 (51.9%)	109 (51.9%)
YAS	99 (48.1%)	101 (48.1%)
Age category (n, %)		
<60	85 (41.3%)	82 (39.0%)
≥60	121 (58.7%)	128 (61.0%)
Gender (n, %)		
Female	110 (53.4%)	110 (52.4%)
Male	96 (46.6%)	100 (47.6%)
Analgesia[1](n, %)		
No	119 (57.8%)	122 (58.1%)
Yes	87 (42.2%)	88 (41.9%)
Weight category (n, %)		
>0 and <70	72 (35.0%)	62 (29.5%)
≥70 and <85	71 (34.5%)	69 (32.9%)
≥85	63 (30.5%)	79 (37.6%)
Baseline utilities[2] (mean (SD)	0.7809 (0.07)	0.7818 (0.08)
Baseline Pain Score	8.8358 (1.19)	8.8469 (1.21)

[1]Administration of IV analgesia prior to randomisation.

[2]Age and gender specific population norm values.

Table 2: Missingness of data by follow-up visit

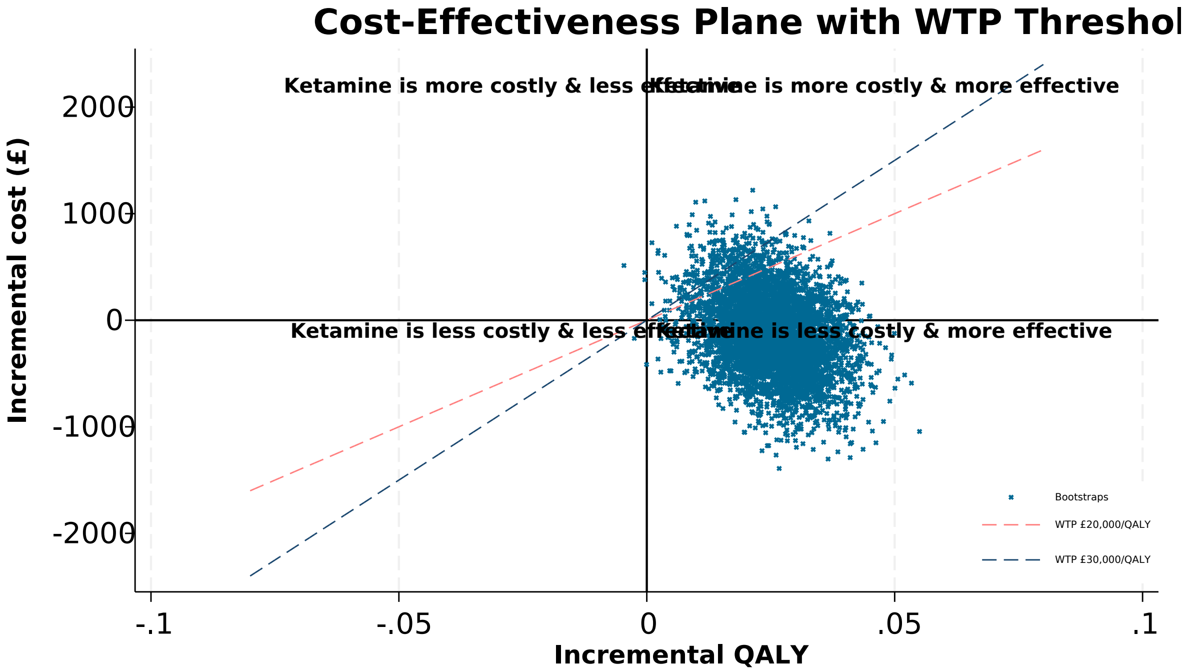
	Ketamine		*Morphine*		*Total*	
	n	**206 (% missing)**	**n**	**210 (% missing)**	**n**	**416 (% missing)**
Health status						
EQ-5D Baseline (derived)	0	(0.00%)	0	(0.00%)	0	(0.00%)
EQ-5D 3 months	92	(44.66%)	99	(47.14%)	191	(45.91%)
EQ-5D 6 months	99	(48.06%)	95	(45.24%)	194	(46.63%)
EQ-5D All visits	108	(52.43%)	112	(53.33%)	220	(52.88%)
Resource use 3months						
Inpatient	89	(43.20%)	93	(44.29%)	182	(43.75%)
Outpatient	88	(42.72%)	93	(44.29%)	181	(43.51%)
Community &PSS	88	(42.72%)	93	(44.29%)	181	(43.51%)
Medication	88	(42.72%)	95	(45.24%)	183	(43.99%)
Special equipment	88	(42.72%)	95	(45.24%)	183	(43.99%)
Wider costs	88	(42.72%)	95	(45.24%)	183	(43.99%)
Resource use 6months						
Inpatient	96	(46.60%)	93	(44.29%)	189	(45.43%)
Outpatient	96	(46.60%)	93	(44.29%)	189	(45.43%)
Community &PSS	97	(47.09%)	93	(44.29%)	190	(45.67%)
Medication	96	(46.60%)	96	(45.71%)	192	(46.15%)
Special equipment	97	(47.09%)	94	(44.76%)	191	(45.91%)
Wider costs	97	(47.09%)	94	(44.76%)	191	(45.91%)

Table 3: Cost-effectiveness results

		Incremental cost (95%CI)	Incremental QALYs (95%CI)	ICER	P[2]	P[3]	NMB[2]	NMB[3]
Base case								
	Imputed costs and QALYs, adjusted[1] (N=416) – 5000 bootstraps	-£116.63 (-£849 to £597)	0.0253 (0.0100 to 0.0406)	-£4982 (Dominates) (SE Quadrant)	0.919	0.959	£631.04	£883.65
Sensitivity analyses								
1	Inclusion of societal costs, imputed and adjusted[1] (N=416)	-£107.31 (-£1326 to £1112)	0.0253 (0.0007 to 0.0500)	-£4242 (Dominates) (SE Quadrant)	0.8610	0.9194	£614.93	£867.57
2	Complete case analysis, adjusted[1] (N=189)	£233.11 (-£783 to £1216)	0.0157 (-0.0131 to 0.0435)	£15,109 (NE Quadrant)	0.5402	0.6216	£74.57	£227.02
3	Baseline utility assumptions changes, imputed and adjusted[1] (N=416)	-£116.63 (-£849 to £597)	0.0253 (0.0100 to 0.0406)	-£5047 (Dominates) (SE Quadrant)	0.9213	0.9605	£632.85	-£885.51
Subgroup analyses								
4	Age <60, imputed and adjusted[1] (N=416)	£791.64 (-£422 to £2005)	0.0192 (-0.0049 to 0.0432)	£41,247 (NE Quadrant)	0.3330	0.4310	-£339.07	-£140.59
5	Age ≥60, imputed and adjusted[1] (N=416)	-£722.78 (-£1610 to £165)	0.0294 (0.0089 to 0.0499)	-£24,561 (Dominates) (SE Quadrant)	0.9940	0.9940	£1310.20	£1604.42
6	Female, imputed and adjusted[1] (N=416)	-£11.92 (-£940 to £916)	0.0090 (-0.0130 to 0.0310)	-£1,356 (SE Quadrant)	0.6180	0.6530	£204.47	£292.29
7	Male, imputed and adjusted[1] (N=416)	-£234.80 (-£1413 to £944))	0.0440 (0.0230 to 0.0660)	-£5,331 (SE Quadrant)	0.9510	0.9790	£1163.44	£1611.50
8	Analgesia no, imputed and adjusted[1] (N=416)	-£474.86 (-£1431 to £481)	0.0240 (0.0027 to 0.0453)	-£19334 (SE Quadrant)	0.9580	0.9660	£996.58	£1239.34
9	Analgesia yes, imputed and adjusted[1] (N=416)	£379.65 (-£768 to £1527)	0.0272 (0.0033 to 0.0511)	£13,854 (NE Quadrant)	0.6050	0.7170	£174.15	£448.63
Scenario analyses		Incremental cost (95%CI)	Incremental effect (95%CI)	ICER				
	[4]Cost per unit change in SPID score, adjusted (N=409)	£436.43 (-£99.96 to £972.83)	0.0979 (-0.4444 to 0.6402)	£4,195 (NE Quadrant)				

All models estimated using SUREG
[1]cost equation adjusted using: Ambulance service (WMAS, YAS), age category (<60, ≥60), gender (male, female), Administration of IV analgesia prior to randomisation (Yes, No), weight (i) >0 and <70, ii) ≥70 and <85, iii) ≥85), QALY equation adjusted using baseline utilities, Ambulance service (WMAS, YAS), age category (<60, ≥60), gender (male, female), Administration of IV analgesia prior to randomisation (Yes, No), weight (i) >0 and <70, ii) ≥70 and <85, iii) ≥85)
[2] probability cost-effective or net monetary benefit at cost-effectiveness threshold of £20,000/QALY. **[3]** probability cost-effective or net monetary benefit at cost-effectiveness threshold of £30,000/QALY
[4]For this analysis costs were restricted to those occurred from randomisation to initial discharge. Pain score was adjusted using Ambulance service, age category, gender, Administration of IV analgesia prior to randomisation, and weight

Figure 1: Cost-effectiveness plane, base case (Imputed costs and QALYs, adjusted)



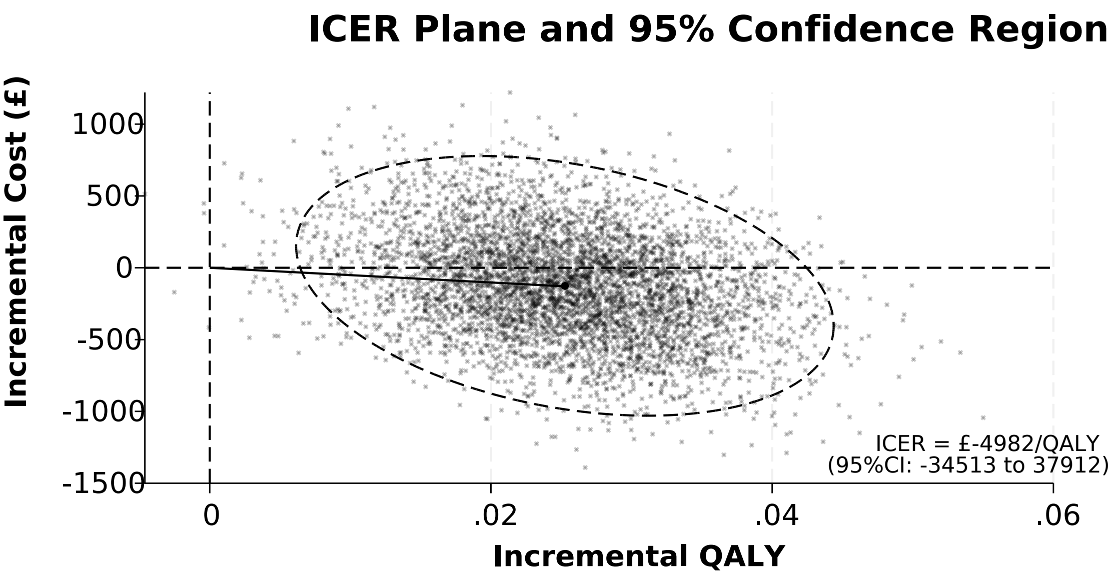
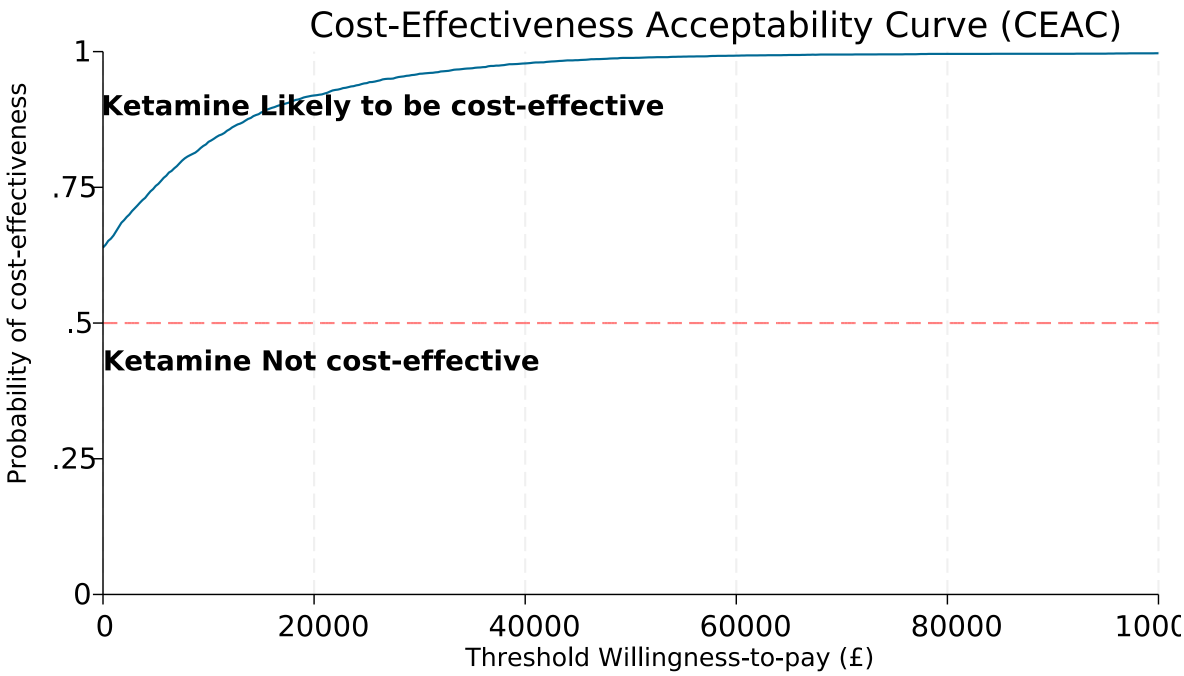
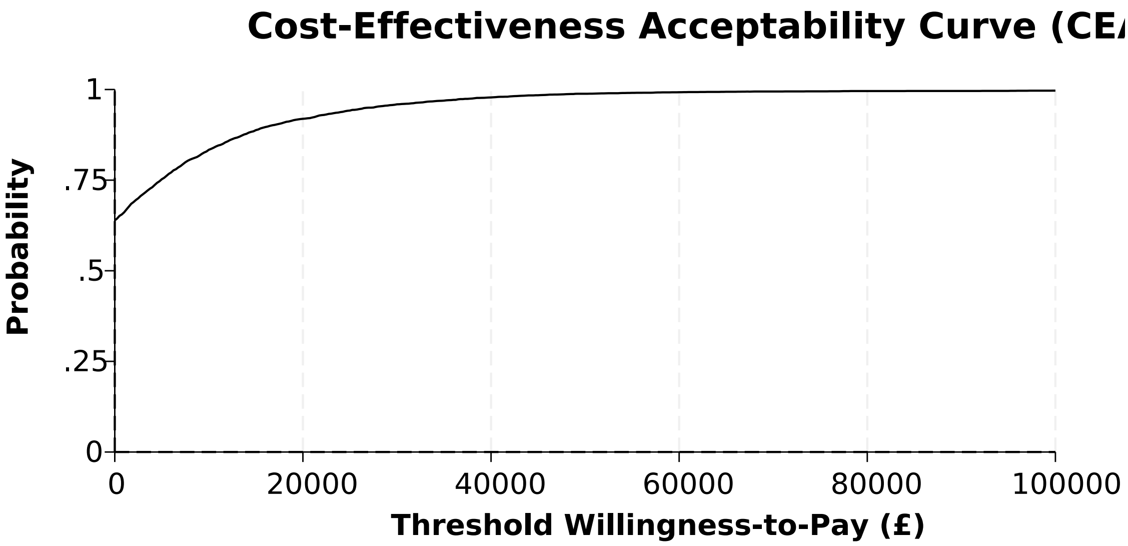


Figure 2: Cost-Effectiveness Acceptability Curve (CEAC), base case (Imputed costs and QALYs, adjusted)


Cost-Effectiveness Acceptability Curve (CEAC)
Ketamine Likely to be cost-effective
Ketamine Not cost-effective
Probability of cost-effectiveness
1
.75
.5
.25
0
0
20000
40000
60000
80000
Threshold Willingness-to-pay (£)


Probability
1
.75
.5
.25
0
0
20000
40000
60000
80000
100000
Threshold Willingness-to-Pay (£)

References

1. Henderson T, Endacott R, Marsden J, Black S. Examining the type and frequency of incidents attended by UK paramedics. Journal of Paramedic Practice. 2019;11(9):396-402.
2. Berben SA, Schoonhoven L, Meijs TH, van Vugt AB, van Grunsven PM. Prevalence and relief of pain in trauma patients in emergency medical services. The Clinical journal of pain. 2011;27(7):587-92.
3. Alonso-Serra HM, Wesley K. Prehospital pain management. Prehospital emergency care. 2003;7(4):482-8.
4. Chambers J, Guly H. The need for better pre-hospital analgesia. Emergency Medicine Journal. 1993;10(3):187-92.
5. 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. Annals of emergency medicine. 1999;34(6):738-44.
6. Kyranou M, Puntillo K. The transition from acute to chronic pain: might intensive care unit patients be at risk? Annals of intensive care. 2012;2:1-11.
7. Jennings PA, Cameron P, Bernard S, Walker T, Jolley D, Fitzgerald M, et al. 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. Emergency Medicine Journal. 2014;31(10):840-3.
8. Brennan F, Carr DB, Cousins M. Pain management: a fundamental human right. Anesthesia & Analgesia. 2007;105(1):205-21.
9. Rivara FP, MacKenzie EJ, Jurkovich GJ, Nathens AB, Wang J, Scharfstein DO. Prevalence of pain in patients 1 year after major trauma. Archives of surgery. 2008;143(3):282-7.
10. Daoust R, Paquet J, Moore L, Emond M, Gosselin S, Lavigne G, et al. Early factors associated with the development of chronic pain in trauma patients. Pain Research and Management. 2018;2018.
11. Williamson OD, Epi GDC, Gabbe BJ, Physio B, Cameron PA, Edwards ER, et al. Predictors of moderate or severe pain 6 months after orthopaedic injury: a prospective cohort study. Journal of orthopaedic trauma. 2009;23(2):139-44.
12. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. The lancet. 2006;367(9522):1618-25.
13. Holbrook TL, Galarneau MR, Dye JL, Quinn K, Dougherty AL. Morphine use after combat injury in Iraq and post-traumatic stress disorder. New England Journal of Medicine. 2010;362(2):110-7.
14. Melcer T, Walker J, Bhatnagar V, Richard E, Han P, Sechriest 2nd V, et al. Glasgow Coma Scale scores, early opioids, and 4-year psychological outcomes among combat amputees. J Rehabil Res Dev. 2014;51(5):697-710.
15. Voscopoulos C, Lema M. When does acute pain become chronic? British journal of anaesthesia. 2010;105(suppl_1):i69-i85.
16. McGreevy K, Bottros MM, Raja SN. Preventing chronic pain following acute pain: risk factors, preventive strategies, and their efficacy. European journal of pain supplements. 2011;5(2):365-76.
17. Committee JRCAL. JRCALC Clinical guidelines 2022: Class Professional Publishing; 2022.
18. 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. Journal of Opioid Management. 2009;5(2):75-80.
19. 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. British Journal of Clinical Pharmacology. 2013;75(5):1340-50.

20. Wong J, Carvalho B, Riley E. Intrathecal morphine 100 and 200 μg for post-cesarean delivery analgesia: a trade-off between analgesic efficacy and side effects. International Journal of Obstetric Anesthesia. 2013;22(1):36-41.
21. Zhou K, Sheng S, Wang GG. Management of patients with pain and severe side effects while on intrathecal morphine therapy: A case study. Scandinavian journal of pain. 2017;17(1):37-40.
22. Shah A. Characteristics of initial prescription episodes and likelihood of long-term opioid use—United States, 2006–2015. MMWR Morbidity and mortality weekly report. 2017;66.
23. Bredmose P, Lockey D, Grier G, Watts B, Davies G. Pre-hospital use of ketamine for analgesia and procedural sedation. Emergency Medicine Journal. 2009;26(1):62-4.
24. Porter K. Ketamine in prehospital care. Emergency Medicine Journal. 2004;21(3):351-4.
25. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. Annals of emergency medicine. 2011;57(5):449-61.
26. Strayer RJ, Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. The American journal of emergency medicine. 2008;26(9):985-1028.
27. McNicol E, Schumann R, Haroutounian S. A systematic review and meta-analysis of ketamine for the prevention of persistent post-surgical pain. Acta Anaesthesiologica Scandinavica. 2014;58(10):1199-213.
28. 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 Anaesthesiologica Scandinavica. 1997;41(9):1124-32.
29. Bansal A, Miller M, Ferguson I, Burns B. Ketamine as a prehospital analgesic: a systematic review. Prehospital and disaster medicine. 2020;35(3):314-21.
30. 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? Emergency Medicine Journal. 2014;31(12):1029-.
31. 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. Emergency Medicine Journal. 2014;31(12):1009-13.
32. 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. The American journal of emergency medicine. 2007;25(4):385-90.
33. 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. Prehospital Emergency Care. 2014;18(2):257-64.
34. Jennings PA, Cameron P, Bernard S, Walker T, Jolley D, Fitzgerald M, et al. Morphine and ketamine is superior to morphine alone for out-of-hospital trauma analgesia: a randomized controlled trial. Annals of emergency medicine. 2012;59(6):497-503.
35. Andolfatto G, Innes K, Dick W, Jenneson S, Zed P, Stenstrom R. P002: Prehospital analgesia with intra-nasal ketamine: a randomized double-blind pilot study. Canadian Journal of Emergency Medicine. 2018;20(S1):S57-S.
36. Johansson P, Kongstad P, Johansson A. The effect of combined treatment with morphine sulphate and low-dose ketamine in a prehospital setting.

Scandinavian journal of trauma, resuscitation and emergency medicine. 2009;17:1-5.
37. NG39 NG. Major trauma: assessment and initial management. Found at: www nice org uk/guidance/ng39/evidence/full-guideline-2308122833 Pages. 2016:236-9.
38. 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). Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine. 2023;31(1):84.
39. NICE U. Guide to the methods of technology appraisal. National Institute for Health and Clinical Excellence (NICE) London, UK. 2022.
40. Jones KC, Burns A. Unit costs of health and social care 2022. 2022.
41. England N. National schedule of NHS costs FY21–22 2022 [Available from: https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/.
42. NICE. British National Formulary [Available from: https://bnf.nice.org.uk/.
43. Digital N. NHS supply chain 2022 [Available from: https://www.supplychain.nhs.uk/.
44. NHSBSA. Prescription Cost Analysis (PCA) data 2022 [Available from: https://www.nhsbsa.nhs.uk/statistical-collections/prescription-cost-analysis-england/prescription-cost-analysis-england-202122.
45. Foundation ER. EQ-5D-5L user guide. EuroQol Research Foundation Rotterdam, The Netherlands; 2019.
46. 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). Quality of life research. 2011;20(10):1727-36.
47. Janssen M, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Quality of life research. 2013;22(7):1717-27.
48. Buchholz I, Janssen MF, Kohlmann T, Feng Y-S. A systematic review of studies comparing the measurement properties of the three-level and five-level versions of the EQ-5D. Pharmacoeconomics. 2018;36(6):645-61.
49. Dritsaki M, Achana F, Mason J, Petrou S. Methodological issues surrounding the use of baseline health-related quality of life data to inform trial-based economic evaluations of interventions within emergency and critical care settings: a systematic literature review. Pharmacoeconomics. 2017;35:501-15.
50. McNamara S, Schneider PP, Love-Koh J, Doran T, Gutacker N. Quality-adjusted life expectancy norms for the English population. Value in Health. 2023;26(2):163-9.
51. Alava MH, Pudney S, Wailoo A. Estimating the relationship between EQ-5D-5L and EQ-5D-3L: results from an English Population Study. The University of Sheffield. 2020.
52. Van Hout B, Janssen M, Feng Y-S, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value in health. 2012;15(5):708-15.
53. Parkin D, Devlin N, Feng Y. What determines the shape of an EQ-5D index distribution? Medical Decision Making. 2016;36(8):941-51.
54. Little RJ, Rubin DB. Statistical analysis with missing data: John Wiley & Sons; 2019.
55. Zellner A, Huang DS. Further properties of efficient estimators for seemingly unrelated regression equations. International Economic Review. 1962;3(3):300-13.

56. Schilling C, Dowsey MM, Clarke PM, Choong PF. Using patient-reported outcomes for economic evaluation: getting the timing right. Value in Health. 2016;19(8):945-50.
57. Ridyard CH, Hughes D. Review of resource-use measures in UK economic evaluations. Unit Costs of Health and Social Care. 2015;2015:22-31.