

Cost effectiveness analysis of intravenous ketorolac and morphine for treating pain after limb injury: double blind randomised controlled trial

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Abstract

Objectives To investigate the cost effectiveness of intravenous ketorolac compared with intravenous morphine in relieving pain after blunt limb injury in an accident and emergency department.

Design Double blind, randomised, controlled study and cost consequences analysis.

Setting Emergency department of a university hospital in the New Territories of Hong Kong.

Participants 148 adult patients with painful isolated limb injuries (limb injuries without other injuries).

Main outcome measures Primary outcome measure was a cost consequences analysis comparing the use of ketorolac with morphine; secondary outcome measures were pain relief at rest and with limb movement, adverse events, patients' satisfaction, and time spent in the emergency department.

Results No difference was found in the median time taken to achieve pain relief at rest between the group receiving ketorolac and the group receiving morphine, but with movement the median reduction in pain score in the ketorolac group was 1.09 per hour (95% confidence interval 1.05 to 2.02) compared with 0.87 (0.84 to 1.06) in the morphine group ($P=0.003$). The odds of experiencing adverse events was 144.2 (41.5 to 501.6) times more likely with morphine than with ketorolac. The median time from the initial delivery of analgesia to the participant leaving the department was 20 (4.0 to 39.0) minutes shorter in the ketorolac group than in the morphine group ($P=0.02$). The mean cost per person was \$HK44 (£4; \$5.6) in the ketorolac group and \$HK229 in the morphine group ($P<0.0001$). The median score for patients' satisfaction was 6.0 for ketorolac and 5.0 for morphine ($P<0.0001$).

Conclusion Intravenous ketorolac is a more cost effective analgesic than intravenous morphine in the management of isolated limb injury in an emergency department in Hong Kong, and its use may be considered as the dominant strategy.

Introduction

Clinical problem

Patients commonly present to accident and emergency departments with severe pain after limb injury and need early treatment with effective analgesia. The use of analgesia in emergency departments and intensive care units may be suboptimal.¹⁻⁴ Some analgesics, such as morphine (the opiate morphine sulphate), have a perceived risk of dependency and therefore, although relatively cheap, are regarded as "dangerous."^{5,6} In repeated frequent doses they may cause dependency, and in single doses they are associated with serious adverse effects that need monitoring and further treatment by both nursing and medical staff. Therefore these drugs, although inexpensive to buy, may have a substantial financial impact on health resources. The impact on emergency departments has never been investigated quantitatively. Non-steroidal anti-inflammatory drugs are also effective at relieving moderate to severe pain and are believed to have fewer adverse effects than opiates.⁷⁻¹⁰ In North America, the United Kingdom, other parts of Europe, and in Hong Kong ketorolac (ketorolac tromethamine) is the only non-steroidal anti-inflammatory drug currently licensed for managing pain by rapid intravenous administration.^{5,10}

Economic problem

A retrospective evaluation of the financial impact of ketorolac in hospital inpatients showed that it was associated with reduced lengths of stay and reduced use of narcotic, antipruritic, and antiemetic drugs.¹¹ These findings were supported by a more specific study that showed that, although ketorolac was an expensive drug, its use for postoperative lumbar spine surgery reduced hospital stay by half a day with substantial financial savings.¹² Both of these studies investigated cost after admission. No studies have investigated the relative economic effect of ketorolac and morphine in emergency departments.

Although intravenous morphine titrated according to the patient's needs is a current recommended gold standard against which all strong analgesics may be evaluated and compared for efficacy and safety,¹ little is known about the economic aspects of its use. The few

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controlled trials comparing doses of intravenous ketorolac and intravenous morphine were all either perioperative studies or associated with cancer.^{8 9 13-20}

We performed a cost effectiveness analysis comparing intravenous ketorolac with intravenous morphine in the management of pain after blunt limb injury (non-penetrating injury to a limb) in an accident and emergency department setting. We hypothesised that, although ketorolac is about three times as expensive as morphine in Hong Kong, ketorolac would be the more cost effective option if all additional related costs were taken into account.

Methods

We conducted the study in the accident and emergency department of the Prince of Wales Hospital, Shatin, a 1400 bed university teaching hospital in the New Territories of Hong Kong. The department receives over 200 000 new patients a year—of whom a fifth are admitted to hospital—and serves a population of about 1 500 000. Currently, health care in the emergency department is free at the point of access, and charges are made only if the patient is admitted to a ward or referred for outpatient follow up.

We obtained ethical approval from the local institutional research ethics committee to conduct a pragmatic, prospective, randomised, controlled, double blind study comparing intravenous ketorolac with morphine in the management of pain after limb injury. We obtained informed written consent from each patient. The study started with a threefold difference in cost between ketorolac and morphine, and we sought to investigate whether the difference was negated when all associated additional costs were included in a cost effectiveness analysis.

Inclusion and exclusion criteria

All patients aged ≥ 16 years presenting to the emergency department between 9 am and 5 pm, Monday to Friday, with an isolated painful limb injury (limb injury without other injury) were considered for the study. The investigators did not consider it reasonable within the study budget to hire a research nurse for 24 hour or evening surveillance. As painful injuries should be treated with analgesia before specific diagnoses are made, recruitment inevitably included some patients with a high clinical probability of a fracture but who subsequently were found to have dislocations or soft tissue injuries alone. All participants were studied on an intention to treat basis, with one exception (see results section), and in the analysis both drug groups were compared to ensure no difference in the proportion with or without fractures. Patients were excluded if they had a history of substance misuse, dementia, indigestion, peptic ulceration or gastrointestinal haemorrhage, recent anticoagulation, pregnancy, adverse reaction to morphine or ketorolac, renal or cardiac failure, hepatic problems, rectal bleeding, recent (<24 hours) use of non-steroidal anti-inflammatory drugs, asthma, chronic obstructive airways disease, chronic pain syndromes, or previous treatment with analgesia for the same injury. They were also excluded if they had a physical, visual, or cognitive impairment, as use of the visual analogue scale would have been unreliable.

Interventions and randomisation

Patients were randomly allocated to one of the two treatment groups by using a random number table.²¹ Ketorolac was prepared as a 2 mg/ml solution and morphine as a 1 mg/ml solution. One group would receive intravenous ketorolac as a 10 mg (5 ml) loading dose over 60 seconds followed by 5.0 mg (2.5 ml) every 5 minutes up to 20 minutes (maximum 30 mg) as required. The other group would receive intravenous morphine as a 5 mg (5 ml) loading dose over 60 seconds followed by 2.5 mg (2.5 ml) every 5 minutes up to 20 minutes (maximum 15 mg) as required. These doses were chosen partly as a result of published reports and partly as a result of the findings from the pilot study (n=40).^{2-4 7-9} Also, the *British National Formulary* recommends that ketorolac should not be administered in an initial bolus of more than 30 mg and that this should not be repeated until a further six hours has elapsed.⁵ Doctors at the Prince of Wales Hospital in Shatin are reluctant to administer more than 15 mg of morphine as an initial slow bolus, so the selected doses were reasonable and practical.

A nurse with clinical responsibilities opened a pre-coded envelope with details of the drug and randomisation number. Either morphine or ketorolac was prepared in the emergency department according to normal practice except that the syringe was labelled with a coded number rather than the drug name. This nurse was not involved in the administration of analgesia, the assessment of the participant, or the treatment of adverse effects. The code was to be broken only if a doctor or other nurse with clinical duties was concerned about severe adverse effects. Both the research nurse, with non-clinical duties, and the participant were blinded to the treatment. The aim was to achieve total pain relief at rest—that is, a pain score of 0—provided that the maximum dose was not exceeded and there were no adverse effects.

Clinical measurements and data collection

A 10 inch (254 mm), numbered (0-10), horizontal, visual analogue pain score was used for baseline measurements and at subsequent time intervals after the first injection.²² A large scale (inches rather than centimetres) was used because disability from poor vision is particularly high in Hong Kong. Routine observations, pain scores, and adverse effects were recorded every five minutes for the first 30 minutes after drug administration, at 30 minute intervals for the subsequent one and a half hours, and once more at six hours. Participants were aware of their previous scores at all stages of recording. The type, number, duration, and severity (based on the Morrow index where appropriate²³) of adverse effects were documented. The physician on duty was free to give extra or alternative doses of analgesia if clinically required, and this was documented. Data were analysed with SAS Statview for Windows, version 5.0 (Abacus Concepts, SAS Institute, Cary, NC, USA).

Clinical and perception outcomes

The primary clinical outcomes were pain relief measured as changes in the pain score, and adverse effects. Pain relief is presented as odds ratios of reaching 50%, 75%, and 100% reduction in pain score (both at rest and with activity) and as median changes in the pain score estimated with the Kaplan-Meier

Table 1 Methods and values for unit costs

Resource item	Method used to measure quantity of resource	Method used to measure price of resource (unit cost of resource, \$HK)
Drugs	Nature and quantity of drugs was recorded by the research nurse	Unit of drug as listed on hospital formulary: ketorolac (30 mg vial) 7.53; morphine (15 mg vial) 2.81; dologesic 32 (tablet) 0.10; lignocaine 1% (2 mg vial) 0.55; pethidine (75 mg vial) 3.00; diclofenac (tablet) 1.00; metoclopramide (10 mg vial) 1.92; naloxone (400 µg vial) 17.80; glyceryl trinitrate (tablet) 0.10
Pharmacy	Estimated time (minutes) required by pharmacist or dispenser to process a unit of prescribed drug: ketorolac (dispenser) 0.34; morphine (pharmacist) 0.30 and (dispenser) 0.23; other non-opioids (dispenser) 0.34; other opioids (pharmacist) 0.30 and (dispenser) 0.34	Pharmacist salary per hour, 552.00; dispenser salary per hour, 180.00
Nursing officer in emergency department	Measured time (minutes) by research nurse for nurses to check and prepare blinded formulation of drug: morphine, 10.20; ketorolac, 7.60	Average nursing officer salary per hour from hospital finance records, 354.00
Registered nurse in emergency department	Time estimated by nurse manager for nurse to deliver drugs in every day setting: morphine, 2.00; ketorolac, 1.00. Measured time (minutes) by research nurse for nurses to manage adverse drug effects from: morphine, 4.40; ketorolac, 7.50	Average registered nurse salary per hour from hospital finance records, 222.00
Emergency room physician	Measured time (minutes) by research nurse for nurses to manage adverse drug effects from: morphine, 1.69; ketorolac, 1.90	Average emergency room physician salary per hour from hospital finance records, 942.00
Inpatient ward costs	No of bed days in observation or hospital ward	Average total daily ward costs from participating hospital, 3650.00
Reattendance costs	Emergency department attendance costs	Average cost per patient per minute, 615.00

£1=\$HK11.

product limit method. “Activity,” for the purpose of this study, involved the research nurse gently moving the injured limb to assess pain. The same nurse performed all movements in a standardised manner. Adverse events were assessed for number, duration, and severity (where applicable). The perception outcome measures were participants’ satisfaction with pain relief and their satisfaction with the care given by staff in the emergency department at the time of discharge from the department.

The end point was six hours after the administration of analgesia if the patient was discharged from the emergency department. To exclude any late effects, however, discharged participants were encouraged to return to the department if they had any adverse events, and computerised records were scanned for returns for up to four weeks after the initial attendance. Four weeks was an arbitrary period, after which any related effects were extremely unlikely. For the patients admitted to hospital, the end point was set at hospital discharge.

Cost measurements and data collection

Costs were calculated according to activities, which included the preparation and administration of analgesics and other drugs, care relating to adverse events, and admission to hospital. We obtained estimates for the time required to use each resource in each activity (table 1) and the unit costs for each of these resources. Drugs were costed separately according to dose, and cost estimates were made for the actual treatment time for adverse events.

Cost effectiveness analysis

The primary efficiency measure was a cost consequences analysis²⁴—that is, a comparison of costs with several different outcomes. Qualitative, rather than quantitative, descriptions were made in comparing outcomes and efficiency measures.²⁵ The sensitivity analysis of cost measures was conducted with regard to observational periods. For the patients who were discharged from the emergency department we

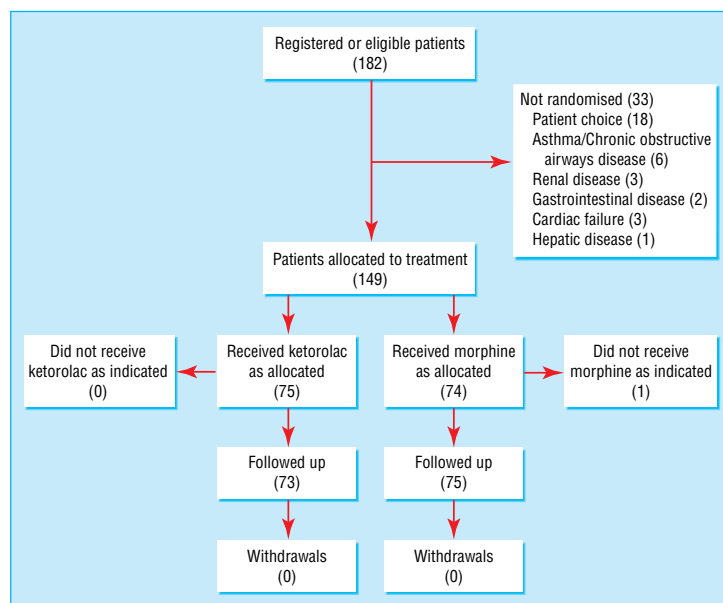
relaxed the assumption that all possible events could be observed within the six hour study period. The true end point, however, may be six hours after the first injection, in which case the previous defined end point would not capture all of the information for the cost effectiveness analysis, especially in those discharged from the emergency department within one to two hours (for whom we assumed that any pain score after the first two hours would be the same for both groups of participants). With the extra four hours of treatment we recalculated the incremental cost effectiveness as stated above.

Statistical analysis

Data were analysed on an intention to treat basis, and we used two tailed tests in all statistical analyses. As pain score and time data did not conform to the Gaussian distribution, non-parametric tests were used to analyse data.²⁶ Baseline characteristics of the two treatments were analysed using the χ^2 test or Mann-Whitney U test.²⁷ Time to event variables were evaluated by using the Kaplan-Meier product limit method, and the log rank test was used to compare the treatment groups.²⁸ A regression line indicating the change in pain score over time was found, and its slope was therefore a summary measure for each patient.²⁹ The median slope for each treatment group was compared and analysed by using the Mann-Whitney U test. The likelihood of achieving pain reduction was presented as hazard ratios.

Results

During the defined study period 182 patients attended the emergency department with acute, painful limb injuries, 149 of whom were allocated to receive blinded analgesia (figure). The 33 patients excluded from the study were excluded for the following reasons: patient decided not to enter the trial (18 patients), asthma or chronic obstructive airways disease (6), renal disease (3), peptic ulceration or gastrointestinal haemorrhage



Flow chart describing progress of patients through randomised trial

(2), ischaemic heart disease (3), liver disease (1). A further patient agreed to enter the trial but was excluded by a visiting doctor who was not familiar with the study. Exceptional circumstances at the time meant that the issue was not resolved, and the patient received alternative drug treatment. The precoded envelope had been opened, but no study analgesia was adminis-

Table 2 Participants' characteristics (n=148). Values are numbers (percentages*) of participants unless stated otherwise

Variable	Ketorolac group (n=75)	Morphine group (n=73)	P value
Mean (SD) age (years)	53.9 (21.7)	53.2 (21.8)	0.85‡
No (%) of men	38 (51)	33 (45)	0.51§
Mean (SD) body mass index (kg/m ²)	22.8 (3.2)	23.0 (3.7)	0.77‡
Mean (interquartile range) time between injury and arrival at hospital (minutes)	95 (30-630)	82 (33-921)	0.75
Cause of injury:			
Motor vehicle crash	6 (8)	4 (5)	0.58¶
Falls	46 (61)	51 (70)	
Crush	20 (27)	14 (19)	
Other	3 (4)	4 (5)	
Fractures:			
Clavicle, humerus, elbow	5 (7)	8 (11)	0.91§
Radius, ulnar	8 (11)	11 (15)	
Hand	15 (20)	13 (18)	
Femur, patella	14 (19)	12 (16)	
Tibia, fibula	5 (7)	3 (4)	
Foot	2 (3)	1 (1)	
Non-fractures:			
Dislocation, upper limb	2 (3)	1 (1)	
Soft tissue injury, upper limb	10 (13)	10 (14)	
Soft tissue injury, lower limb	14 (19)	14 (19)	
Initial mean (SD) pain score:			
At rest	3.8 (1.1)	3.9 (1.1)	0.65‡
With activity	8.1 (1.2)	8.1 (1.2)	0.85‡
Referred for orthopaedic assessment	41 (55)	36 (49)	0.52§
Admitted to hospital†	38 (51)	29 (40)	0.18§
Admitted with adverse effects	0	3 (4)	

*Percentages may not sum to 100 because of rounding.

†Patients admitted to hospital (to orthopaedic or emergency observation ward).

‡‡ test for unpaired means comparison.

§ χ^2 test.

¶Fisher's exact test.

tered. This patient was therefore excluded from the analysis because he received no study analgesia. In another case, the code was broken by an attending physician because the participant (in the morphine group) showed signs of severe drowsiness. All data were collected and the participant was included in the analysis.

Baseline characteristics and clinical outcomes

Baseline characteristics of the 148 participants in the two groups were similar (table 2). Seventy seven patients were admitted to hospital—71 to an orthopaedic ward for orthopaedic reasons and not because of adverse events after analgesia and 6 to the emergency ward. One participant (from the ketorolac group) was admitted for four days not because of adverse events after analgesia but because of poor social circumstances and immobility. Five participants were admitted from the morphine group (median stay 1 day)—two because of poor social circumstances and mobility and three because of adverse events after analgesia (dizziness, drowsiness, and vomiting).

According to the doses and methods used in this study, the odds of achieving 50%, 75%, and 100% pain relief at rest favoured morphine, although these results were not statistically significant ($P > 0.05$) (table 3). With activity, the odds of achieving 50% and 75% pain reduction favoured ketorolac, although only the result for 75% pain reduction was statistically significant ($P < 0.05$) (table 3). The median rate of a decrease in pain score was greater with ketorolac than with morphine (table 4). Ten minutes after the start of analgesia there was a 20% reduction in pain score for ketorolac and 32% for morphine at rest and a 27% reduction in pain score for both ketorolac and morphine with activity (data not shown).

Participants were 16 times more likely to develop adverse effects with morphine than with ketorolac (table 5), with an odds ratio of 144.2 (95% confidence interval 41.5 to 501.6; $P < 0.0001$). The commonest adverse effects are shown in table 5, but in addition, there were reports of sweating (5 participants), rashes (3), abdominal pain (3), breathlessness (2), and dry mouth (1) in morphine group and of dry mouth (1) in the ketorolac group. No participants reported headache, wheeze, chest tightness, indigestion, or gastrointestinal haemorrhage. Morrow index scores for morphine and ketorolac were 0.37 (0.23 to 0.50) and 0.004 (0.001 to 0.01) respectively for dizziness ($P < 0.001$); 0.56 (0.30 to 0.83) and 0 respectively for nausea ($P < 0.001$); and 0.43 (0.14 to 0.71) and 0 respectively for vomiting ($P < 0.001$).

No difference was found between the two drugs for time between injury and arrival at the emergency department (table 2) or for time between arrival at the emergency department and prescription of analgesia, preparation of analgesia, or time taken for radiography (table 6). Participants waited longer (between prescription and administration of initial bolus) to receive morphine than ketorolac ($P = 0.0002$) and therefore spent longer in the emergency department, although total time spent in the emergency department was not statistically significant ($P = 0.11$). The total time that nurses and doctors spent managing adverse effects was also longer for the morphine group than for the ketorolac group (table 7).

For morphine, the dose administered divided by body mass index (weight(kg)/(height(m)²)) correlated with time to complete pain relief at rest (Spearman's rank correlation $r_s=0.552$, $P<0.0001$), but little effect was seen with ketorolac ($r_s=0.250$, $P=0.03$). For morphine, the dose administered divided by body mass index correlated weakly with duration of vomiting ($r_s=0.311$, $P=0.008$). Correlations between age and pain score and between age and duration of vomiting were weak ($r_s<0.400$).

Cost analysis

Marginal costs were used to measure the difference in costs between the two interventions (table 7). The mean cost per person, excluding admissions, was \$HK43.60 (£4; \$5.6) for those in the ketorolac group and \$HK228.80 for those in the morphine group ($P<0.0001$). Overall mean cost per person, including admissions unrelated to analgesia, was \$HK11 361.20 for those in the ketorolac group and \$HK7279.62 for those in the morphine group ($P=0.451$). If admission costs are excluded, much of the difference between the costs for the two groups was the result of the management of adverse effects.

Cost effectiveness

When we included admission costs we observed no significant differences in costs between the two groups. We found a significant reduction in pain with activity in the ketorolac group and significantly fewer common adverse events. Additionally, the participants in the ketorolac group showed a greater degree of satisfaction with that drug than the participants in the morphine group showed with their drug (table 8). Ketorolac administration therefore is the "dominant" strategy, with significantly better outcomes, lower costs when costs for the emergency department and pharmacy are combined, but not significantly higher overall costs.

Discussion

This study shows that, although intravenous morphine costs less than intravenous ketorolac in Hong Kong, ketorolac is a cheaper option than morphine once all additional costs incurred by the accident and emergency department and the pharmacy are taken into account. When admission costs are included, however, the difference in cost is not significant. When both drugs are administered intravenously in titrated doses according to individual patients' needs, ketorolac is at least as efficacious as morphine and may afford a small advantage when the injured limb is moved. Ketorolac had fewer adverse effects than morphine, made fewer

Table 3 Likelihood of achieving pain reduction

Activity level	Hazard ratio*	P value†
At rest:		
50% reduction in pain	0.83 (0.60 to 1.15)	0.271
75% reduction in pain	0.84 (0.60 to 1.16)	0.279
Complete pain relief	0.93 (0.66 to 1.30)	0.654
With activity:		
50% reduction in pain	1.18 (0.85 to 1.63)	0.330
75% reduction in pain	1.49 (1.05 to 2.12)	0.027

* >1 means that ketorolac performed better than morphine for pain relief.

†Wald test.

Table 4 Summary results for median rate of decrease in pain score per hour (95% confidence intervals)

	Ketorolac (n=75)	Morphine (n=73)	P value*
At rest	11.40 (9.41 to 12.77)	10.80 (10.20 to 13.54)	0.540
With activity	1.09 (1.05 to 2.02)	0.87 (0.84 to 1.06)	0.003

*Mann-Whitney U test.

Table 5 Numbers (percentages) of participants with adverse events*

Variable	Ketorolac group (n=75)	Morphine group (n=73)	P value†
Total‡	4 (5)	65 (89)	<0.0001
Drowsiness	1 (1)	43 (59)	<0.0001
Sleeping	0	8 (11)	0.0054
Dizziness	2 (2)	55 (75)	<0.0001
Nausea	0	27 (37)	<0.0001
Vomiting	0	12 (16)	<0.001
Phlebitis	0	20 (27)	<0.0001

*Some participants reported more than one adverse effect.

†Fisher's exact test.

‡Includes participants with uncommon adverse effects that are noted in the text but not in the table.

demands on doctors' and nurses' management time, resulted in earlier discharge or admission to a ward, and was associated with greater satisfaction among patients. Morphine may afford a small clinical advantage, however, with better odds of relieving pain at rest than with ketorolac.

Originality of study

The study has the several original aspects. Firstly, it compares intravenous ketorolac and intravenous morphine in a nurse controlled, analgesic regimen with titrations according to the individual patients' needs. None of the many other studies that have compared parenteral ketorolac with parenteral opiates in a variety of settings^{7-10 13 15-20 30-41} has compared one drug with the other as in this protocol. Secondly, the two drugs were studied within the context of an emergency department. Both morphine and ketorolac have been studied separately in emergency departments in both controlled and uncontrolled studies,^{10 30 42} but no study has compared one with the other in this setting.

Table 6 Median number (interquartile range) of minutes relating to participants' treatment

Variable	Ketorolac group (n=75)	Morphine group (n=73)	Median difference (95% confidence interval)	P value*
Interval between arrival in emergency department and doctor prescribing analgesia	38.0 (30.0 to 54.0)	39.0 (29.0 to 53.0)	1.0 (-5.0 to 7.0)	0.72
Preparation for analgesia	5.0 (5.0 to 10.0)	10.0 (5.5 to 12.5)	2.0 (0 to 5.0)	0.0002
Undergoing radiography	5.0 (5.0 to 10.0)	5.0 (4.0 to 10.0)	0 (-1.0 to 0)	0.75
Total time spent in emergency department	155.0 (112.0 to 198.0)	171.0 (126.0 to 208.5)	15.0 (-4.0 to 33.0)	0.11
Interval between receiving analgesia and leaving emergency department	115.0 (75.0 to 149.0)	130.0 (95.0 to 170.0)	20.0 (4.0 to 39.0)	0.02

*Mann-Whitney U test.

Table 7 Analysis of all costs incurred in treating participants

Variable	Ketorolac group (n=75)				Morphine group (n=73)			
	Unit cost (\$HK)	No of participants receiving service	Mean duration of service received (minutes)	Average cost per person (\$HK)	Unit cost (\$HK)	No of participants receiving service	Mean duration of service received (minutes)	Average cost per person (\$HK)
Drug costs								
Analgesia	7.53	75	NA	7.53	2.81	73	NA	2.81
Professional fee for analgesia	1.02	75	NA	1.02	3.44	73	NA	3.44
Extra analgesia:								
Dologesic 32 (per tablet)	0.10	12	NA	0.02	0.10	19	NA	0.03
Lignocaine 1% (per 2 ml vial)	0.55	4	NA	0.03	0.55	8	NA	0.06
Pethidine (per 75 mg vial)	3.00	3	NA	0.12	3.00	1	NA	0.04
Diclofenac (per tablet)	1.00	3	NA	0.04	1.00	1	NA	0.01
Professional fee for extra analgesia:								
Non-opioid drug	1.02	18	NA	0.25	1.02	28	NA	0.39
Opioid drug	3.44	3	NA	0.14	3.44	1	NA	0.05
Drugs to treat adverse events:								
Metoclopramide (per 10 mg vial)	1.92	0	NA	0	1.92	17	NA	0.45
Naloxone (per 400 µg vial)	17.8	0	NA	0	17.80	5	NA	1.22
Glyceril trinitrate (per tablet)	0.10	0	NA	0	0.10	1	NA	0.01
Professional fee for adverse effects of drugs:								
Non-opioid drug	1.02	0	NA	0	1.02	22	NA	0.31
Opioid drug	3.44	0	NA	0	3.44	0	NA	0
Human resources costs								
Nursing time:								
To prepare drug	3.70	75	7.64	28.27	3.70	73	10.16	37.59
To deliver drug	3.70	75	1.0	3.70	5.90	73	2.0	11.80
To manage adverse effects of drugs	3.70	4	7.26	1.43	3.70	65	4.37	14.40
Doctors' time to manage adverse effects of drugs	15.70	4	1.25	1.05	15.70	65	1.72	24.04
Reattendance costs	615.00	0	NA	NA	615.00	1	NA	8.45
Admission costs for adverse events (per day)	3010.00	0	NA	NA	3010.00	3	1†	123.70
Other admission costs (per day)	3010.00	38	7.42	11 317.60	3010.00	29	5.90	7050.82
Total average (SD) cost per person								
Excluding "other admission costs"				43.60 (22.26)	228.80 (655.01)*			
Including "other admission costs"				11 361.20 (17 470.65)	7279.62 (12 500.68)			

£1=\$HK11.

NA=not applicable.

Professional fee refers to the pharmacy costs in processing and checking the drugs.

*Mann-Whitney U test, P<0.0001.

†1 day.

Thirdly, a cost effectiveness analysis drew together the strands of efficacy, adverse effects, resource demands, and participants' satisfaction. Other studies have shown that ketorolac may be as efficacious as morphine and tolerated better, but none has examined the issue in a broader economic context.

Study protocol versus routine practice

This study differs from normal emergency department practice in several respects. In normal practice no delay occurs as a result of patient information and consent procedures. The delay in this study was kept to an absolute minimum, and no complaints were received from patients or relatives. Secondly, in normal practice, analgesia is not given in a blinded regimen and patients are not observed and questioned closely by a research nurse. Some degree of artificiality has to be accepted if vital data are to be recorded. As the study was randomised and double blind, however, any deviations from normal should at least be the same for both

groups, leaving the effect of the two analgesics as the only difference in outcome.

Strengths and shortcomings

The strengths of the study lie in its randomised controlled design, delivery of analgesia according to individual needs, and its attempt to reflect the real world as far as reasonably possible. The economic evaluation follows recent guidelines published in the *BMJ*.⁴³⁻⁴⁵ Although every effort was made to blind both the research nurses and the participants to treatment, certain clinical clues—such as pinpoint pupils—might reveal the identity to discerning medical and paramedical staff. This is a shortcoming that is probably unavoidable and applies to all double blind studies comparing opiates with other drugs. In an ideal double blind regimen, treatment should not be prepared anywhere near the scene of research, so that contamination is completely impossible. In this study, nurses prepared the drugs within the department and

Table 8 Participants' satisfaction with analgesia and with emergency department management

Variable	Median (interquartile range)		Median difference (95% confidence interval)	P value*
	Ketorolac group	Morphine group		
Satisfaction with analgesia	6.0 (5.0-6.0)	5.0 (4.0-6.0)	1.0 (1.0-2.0)	<0.0001
Satisfaction with emergency department management	6.0 (5.0-7.0)	6.0 (5.0-6.0)	0	0.30

*Mann-Whitney U test.

used normal stock. This was important if we were to monitor the “real” time taken to prepare drugs for delivery and the different grades of nurses taking part in the process. The delay in starting to administer morphine compared with ketorolac was due to the extra checking procedures necessary for administering opiates.

Although more participants were admitted to hospital in the ketorolac group, the overall greater costs were not significant. No participant was admitted to an orthopaedic ward because of adverse drug effects (admission was principally for management of the injured limb). Only three of the six participants observed in an emergency observation ward were admitted specifically for adverse effects, and all were in the morphine group. Admission costs are much greater and more variable than for analgesia and associated drugs, which may explain why, when all additional costs are included, no difference was found between the two treatments. Others have noted that non-urgent visits to emergency departments cost relatively little when compared with the cost of admission.⁴⁶

Baseline pain scores at rest were not high, and it may be argued that many of the participants did not need strong analgesia. With only minor degrees of movement, however, the average pain score rose to over 8 (out of a possible 10), showing that these participants did experience severe pain and that the administration of strong analgesia was appropriate. We could not study a placebo effect as it would have been both unethical and unjustified to deny some participants appropriate analgesia when they were in moderate to severe pain. Limb injuries are clearly painful, however, and most participants in this study had fractures confirmed by radiography. The reductions in pain score exceeded the minimum required for clinical significance.^{47 48}

The primary aim of this study was to investigate costs related to the input from the emergency department to pain management, but to follow any prolonged or delayed adverse events we had to extend data collection beyond the emergency department. No attempt was made to evaluate subsequent analgesia. Principal adverse events included drowsiness, sleeping, dizziness, nausea, vomiting, and phlebitis. These events occurred in a greater proportion of participants (and with greater severity and duration) in the morphine group than in the ketorolac group. Adverse events drain nursing resources, which during busy periods would be better used elsewhere. No cases of serious adverse effects, such as gastrointestinal haemorrhage, occurred in this study, which may be partly the result of the stringent exclusion criteria. One case of a serious adverse effect in either the morphine or the ketorolac group might dramatically alter the relative cost of each drug. It is difficult to assess the relative cost of rare drug reactions in any study, but provided that care is taken to exclude high risk subjects, then serious adverse effects should be few. In a post-marketing surveillance study the risk of gastrointestinal complications after intravenous ketorolac was low especially when treatment was limited to less than five days.⁴⁹ Few patients were excluded from our study on the basis of an existing medical illness, showing that this study has relevance to

most adults presenting to emergency departments with isolated painful limb injury.

Routinely administering an antiemetic with an opiate such as morphine might reduce adverse events with overall lower costs, and if lower doses of morphine were administered fewer adverse events might have occurred. However, the correlation between morphine dose and pain relief suggests that lower doses would have resulted in reduced analgesic effect. The poor correlation between morphine dose and vomiting also suggest that small reductions in the dose would not have influenced the duration of this adverse effect. It is surprising that there was no difference in age between the two groups. Any relation between perception of pain and age in this study was weak. Also, a relation between age and adverse events was not evident. The study protocol was designed such that reduced doses of analgesia would be given if adverse events arose, which may account for the poor correlation with age.

The time spent ordering, delivering, and controlling stock has not been taken into account as many other drugs are involved in those processes, and the contribution of ketorolac and morphine could not be evaluated separately. Average salaries of nurses and doctors have been used as a cost reference, but in real life more junior or senior staff may have a greater actual involvement.

Participants were studied between 9 am and 5 pm and only on weekdays. It is therefore unclear whether out of hours ratios of staff to patients, case mix, and demand would affect the results. Emergency departments function on a priority system, whereby the efficiency of processing an individual patient depends on the number of patients with higher priority in the department at a given time and the available resources. This study did not address the difficult and complex relations between the individual patient and the total demand on the rest of the department at the time that patient attended. If it is assumed that staff are always doing something useful while at work, then minutes of freedom from managing one patient means that other duties may be attended to, and this has an impact on cost effectiveness.

It is difficult to know how far these results may be applied to settings outside Hong Kong. If one assumes, however, that the difference in costs between ketorolac and morphine is 7.5-fold rather than 2.5-fold, that doctors and nurses salaries are a third of those in Hong Kong, and that all other variables are the same, then ketorolac and morphine are equally cost effective (data not shown).

Implementing results

The management of pain remains one of the great challenges for emergency departments worldwide, and so policies on rapid, cost effective, and safe analgesia are essential for good patient care and patient satisfaction. High demand and prolonged waiting times also provide a drain on emergency departments' resources, and so any intervention that reduces the time that patients spend in the department is also important. This study showed that intravenous ketorolac is more cost effective than intravenous morphine in the management of acute pain after blunt limb injury in an emergency department. Doctors may be more confident about using an effective analgesic with no

What is already known on this topic

Intravenous morphine sulphate is generally as effective as intravenous ketorolac tromethamine for surgical and cancer related pain

Morphine may cause more adverse events than ketorolac

No cost effectiveness analyses have compared the use of intravenous ketorolac and morphine titrated according to patient needs and none has evaluated such use in emergency departments

What this study adds

For limb injury in an emergency department ketorolac is as effective as morphine for pain at rest; for pain with movement, however, ketorolac may be marginally better than morphine

Ketorolac produced fewer, less severe, and shorter adverse events than morphine

Participants receiving ketorolac left the emergency department sooner than those receiving morphine

Ketorolac is a more cost effective analgesic than morphine in this setting and is associated with greater patient satisfaction

risk of dependence, fewer adverse effects, reduced arrival to discharge times in their departments, and reduced costs. These results are relevant to emergency departments in Hong Kong and are likely to be applicable to other systems that are organised along similar lines. Differences in staff salaries and other costs, however, may limit the application of our findings to some environments.

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