A randomised-controlled trial of paracetamol and ibuprofen with or without codeine or oxycodone as initial analgesia for adults with moderate pain from limb injury.

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All authors contributed equally to the concept, design and conduct of the study. JP oversaw study drug preparation and distribution to all sites. DE-W, RM and AM were particularly responsible for study conduct at the Monash, Dandenong and Casey sites. AG was responsible for collation of data from each site and data entry. AG and RM were responsible for data analysis. All authors contributed to interpretation of findings and manuscript preparation. AG takes overall responsibility for the manuscript.

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A randomised controlled trial of paracetamol and ibuprofen with or without codeine or oxycodone as initial analgesia for adults with moderate pain from limb injury.

ABSTRACT:

Objective: Compare pain relief from non-opioid, codeine and oxycodone analgesic regimens in adults with moderate pain from limb injury.

Method: Double-blind, randomised, controlled, non-inferiority trial. Three regimens of six tablets: each included 2x500mg paracetamol and 2x200mg ibuprofen with either 2x100mg thiamine (non-opioid), 2x30 mg codeine (codeine) or 2x5 mg oxycodone tablets (oxycodone). Primary outcome: difference in mean VAS change between groups at 30 minutes, with a limit of inferiority of 13. Secondary outcomes included mean change in VAS rating from baseline to 30 minutes for each group, patient satisfaction, need for additional analgesia and adverse events. Pain ratings taken at 60 and 90 minutes for patients still in ED are described.

Results: Of 182 patients randomised, non-opioid, codeine and oxycodone numbers were 61, 62 and 59. Differences (95% CI) between groups at 30 minutes were: non-opioid versus codeine -2.6 (-8.8 to 3.6); non-opioid versus oxycodone -2.7 (-9.3 to 3.9); codeine versus oxycodone 0.1 (-6.6 to 6.4). Mean VAS reductions for non-opioid, codeine and oxycodone were -13.5, -16.1 and -16.2 mm respectively. Satisfaction with analgesia was reported by 77.6% (64.7 – 87.5), 81.0% (67.2 – 89.0) and 73.6% (59.7 – 84.7), and adverse events by 3.3% (0.4 – 11.3), 1.6% (0.4 – 8.7) and 16.9% (8.4 – 29.0) respectively. Mean VAS reductions at 60 and 90 minutes were -23.2 and -18.7 mm for non-opioid, -30.7 and -33.3 mm for codeine and -26.1 and -31.7 mm for oxycodone.

Conclusion: At 30 minutes, analgesic effects of non-opioid, codeine and oxycodone groups were non-inferior.

Key words:

Analgesia, emergency department, trauma, clinical efficacy, randomised controlled trial, paracetamol, ibuprofen, opioid

A double-blind, randomised controlled trial of paracetamol and ibuprofen with or without codeine or oxycodone as initial analgesia for adults with moderate pain from limb injury.

INTRODUCTION

Early and adequate pain management is considered a fundamental component of Emergency Department (ED) patient care.¹ Following introduction of Australian guidelines recommending analgesia within 20 minutes of hospital arrival,² our organisation implemented standing order nurse-initiated analgesia, following the principles of the World Health Organisation analgesia ladder.³ Our analgesic regimens for severe pain (parenteral opioids) and mild pain (oral paracetamol or ibuprofen) are unambiguous, but lack of evidence meant that the best approach to moderate pain was unclear.

Limited analgesic studies for ED patients with moderate pain from acute injury, suggest that a paracetamol and non-steroidal anti-inflammatory drug (NSAID) combination may provide greater pain relief than single NSAID or paracetamol regimens,⁴ and that codeine has no greater effect as a single agent in comparison with paracetamol or ibuprofen for children.⁵ The more extensive post-operative analgesia research also generally supports that combination regimens of NSAIDs and paracetamol may be more effective than single agents for moderate pain, with additional benefits from oral opioids being uncertain.⁶⁻¹²

For these reasons, in adults with moderate pain from limb injury, we aimed to compare a single-dose regimen of paracetamol and ibuprofen, against this combination with the addition of either codeine or oxycodone. The study hypothesis was that all three regimens would result in a clinically significant reduction in pain, and that no combination would be

inferior to any other. Such a finding would support the standing order for moderate pain commencing with a non-opioid combination regimen.

METHOD

Study design: Double-blind, randomised, controlled, non-inferiority trial with three parallel arms, utilising a convenience sample of patients. The trial was approved by the Monash Health Human Research and Ethics Committee and is registered as a clinical trial with the Australian and New Zealand Clinical Trials Registry (ACTRN12610000588099).

Study setting and period: The study was conducted in Melbourne, Australia, at the three Monash Health EDs: Casey Hospital (annual census 52,000 patients), Dandenong Hospital (annual census 57,000 patients) and Monash Medical Centre (annual census 62,000 patients). Patients were recruited between October 1 2010 and October 31 2013.

Study drug regimens: The three drug regimens, each containing six tablets, are shown in Box 1. Thiamine, a B-group vitamin with no known analgesic effect, was chosen as a dummy preparation due to its similar appearance to both the oxycodone and codeine tablets, so that tablet numbers were the same.

Randomisation and concealment: Patients were randomised in blocks of 18. An independent pharmacist performed the randomisation and prepared all study medications. Tablets were placed in opaque containers, which were sealed and labelled as 'Study Drug'. Administration instructions, expiry date and a unique study ID number were attached. Participants were asked to ingest the tablets directly from the opaque container, so that they were not seen.

Measurement tools: Pain severity was rated on a Visual Analog Scale (VAS). The standard 100 mm line was marked 'No pain' at the left and 'Worst pain imaginable' at the right. Measurements were taken from the left, and change was reported as negative for reductions. Change in severity from baseline was rated as: 'a lot less', 'a little less', 'the

same', 'a little more' or 'a lot more'. Patient satisfaction was recorded as 'satisfied', 'not satisfied' or 'unsure'.

Primary outcome measure: Difference in mean VAS change between groups at 30 minutes.

Secondary outcome measures: 1) Change in VAS rating from baseline to 30 minutes for each group. 2) Percentage of patients at 30 minutes who had improved symptoms ('a lot less' or 'a little less') 3) Number of patients requiring additional analgesia. 4) Satisfaction with initial analgesia. 5) Symptom improvement, VAS change from baseline to 60 and 90 minutes, and adverse events are described.

Inclusion criteria: Age 18 to 75 years; acute limb injury (previous 48 hours); moderate pain on arrival (numerical rating 4 to 7 on a 0 to 10 scale); oral analgesia deemed suitable. Two changes were made to the initial inclusion criteria. The initial upper age limit had been 65 years, due to a concern that older people might not understand the VAS; as this concern was unsupported, the upper age limit was increased to 75 years in Feb 2012. The initial time from injury had been restricted to less than eight hours; this was increased to less than 48 hours in Feb 2012. This was felt to be more in-line with definitions of "acute pain" used elsewhere.⁵

Exclusion criteria: Need for time critical interventions (e.g. reduction of dislocations); digital injuries (treated with nerve blocks); pregnant and breastfeeding women; NSAID sensitive asthma; active peptic ulcer disease; known renal impairment; acute intoxication (any substance); use of any analgesic or sedating agent in the preceding four hours; regular use of analgesic agents for chronic pain; allergy or intolerance to paracetamol, opioids, or NSAIDs; inability to take oral medications; inability to understand the study explanation (any reason); unwillingness to comply with recommendations to not drive, consume alcohol or operate machinery for at least eight hours after being given the study medication.

Study procedure: The triage nurse screened patients for recruitment by a duty ED doctor at any time of the day. Following consent, an initial VAS rating was recorded, a numbered study medication container obtained and the medication administered. After 30 minutes, a

VAS rating was repeated and symptom change reported. Need for additional analgesia was assessed, and administered at the discretion of the treating doctor. If the patient was still in the ED at 60 and/or 90 minutes, repeat ratings were recorded and timing of additional analgesia noted. Patients were not detained in the ED for these ratings, if their episode of care was complete. Satisfaction with initial analgesia and adverse events were recorded prior to ED discharge. To confirm blinding, the participant and treating doctor were asked to nominate which study drugs had been administered, if they believed they knew.

Limb injuries were otherwise managed as required, and patients discharged from the ED with analgesia based on the recommendation of the treating doctor. Study participants were not contacted after they left the ED.

Statistical analysis: Initial pain ratings are reported as median with interquartile range (IQR). As the distribution of data for change in VAS approximates normal, these are reported as mean change (mm) with 95% confidence intervals (CI). Change is reported for each group from enrolment to each time point, as is the difference between each pair of treatment regimens at 30 minutes. Description of symptom change was dichotomized to symptom improvement ('a lot less' or 'a little less') versus no improvement. Agreement between suspected and actual study drug identity, by patients and doctors, is reported using the kappa statistic. Analyses were performed using Stata statistical software (v8.0; StataCorp, College Station, TX, USA).

Sample size: Two previous ED based analgesic RCTs reported mean VAS changes at 30 minutes of about -10 mm (SD +/-20) for single drug regimens of paracetamol, NSAID and codeine.⁴⁻⁵ The generally accepted minimum clinically significant difference (MCSD) of 13 mm,¹³⁻¹⁴ was nominated as the limit of inferiority, since a lesser difference between groups is unlikely to be clinically important to the patient. Assuming an SD +/-20, and a difference in mean VAS change of zero between groups, a sample of 40 patients per group would be required (alpha 0.05, beta 0.90) to demonstrate non-inferiority. Due to the uncertainty of these assumptions, it was decided to allow a large margin for error by aiming to recruit 72 patients per group.

RESULTS

During the 1,127 day study period, a total of 13,290 appropriately aged patients presented with a diagnosis of limb fracture or soft tissue injury, and had a pain score of 4 – 7 recorded at some time during their episode of care. A random sample of 133 of these patient records (1% of the total) was examined in detail. Of these, 34 (25.6%) proved to be eligible.

Reasons for exclusion, and a comparison of baseline characteristics with the recruited patients are shown in the Appendix. This suggests that about 3,400 eligible patients may have presented during the study period.

A total of 185 patients were recruited, representing about 5 to 6% of the probable eligible population. Of these, 182 (98.4%) were available for analysis, with 62, 67 and 53 from Monash, Dandenong and Casey Hospitals respectively. Of these, 61 (33.5%), 62 (34.1%) and 59 (32.4%) were randomised to the non-opioid, codeine and oxycodone groups, respectively. There were no differences in baseline variables between sites or treatment groups (Table 1).

Patient flow is shown in Figure-1. Prior to the alteration of age-related and time since injury inclusion criteria, 26 (14.3%) of the patients had been recruited, nine each in the non-opioid and oxycodone groups, and eight in the codeine group. The difference in median age of participants, before and after the alteration, was not statistically significant, being 28.5 (IQR: 21 – 41) versus 33 (IQR: 23 – 45.5) years, $p = 0.24$ Mann Whitney). The difference in median time since injury, before and after the alteration, was statistically significant, being 90 (IQR: 49 – 210) versus 250 (IQR: 60 – 960) minutes, $p = 0.001$ Mann Whitney). Difference in time since injury was not statistically significantly between the three study groups, either before or after the alteration, or for the entire study period.

At 30 minutes, the mean VAS reductions for the non-opioid, codeine and oxycodone groups were -13.5 mm, -16.1 mm and -16.2 mm respectively. The difference in mean change was: -2.6 (95% CI: -8.8 to 3.6) for non-opioid versus codeine; -2.7 (95% CI: -9.3 to 3.9) for non-opioid versus oxycodone; 0.1 (95% CI: -6.6 to 6.4) for codeine versus oxycodone. The

rating change for each patient from time-0 to 30 minutes is illustrated in Figure 2. The difference in mean change between the treatment groups at 30 minutes is shown in Figure 3.

Symptom change at 30 minutes was described by 58/61 (95%), 56/62 (90%) and 55/59 (93%) of the non-opioid, codeine and oxycodone groups respectively, and additional analgesia was received by 3/182 (1.6%). Symptom improvement at 30 minutes was reported by 40/58 (69.0%, 95% CI: 55.5 – 80.5), 39/56 (69.6%, 95% CI: 55.9 – 81.2) and 38/55 (69.1%, 95% CI: 55.2 – 80.9) for the non-opioid, codeine and oxycodone groups, respectively.

Satisfaction with initial analgesia was reported by 58/61 (96%), 58/62 (94%) and 53/59 (90%) of the non-opioid, codeine and oxycodone groups. Rescue analgesia was given to 11/61 (18.0%), 7/62 (11.3%) and 2/59 (3.4%) respectively. Adverse events were reported for 13/182 (7.1%). Details of these secondary outcomes, and the time points at which they were recorded are shown in Table-2.

At 60 minutes, VAS ratings were performed by 49/61 (80%), 49/62 (79%) and 47/59 (80%) of the non-opioid, codeine and oxycodone groups. The mean VAS reductions from baseline to 60 minutes were -23.2 mm, -30.7 mm and -26.1 mm respectively. When recorded, symptom improvement was reported by 31/44 (70.5%), 34/44 (77.3%) and 37/45 (82.2%) respectively.

At 90 minutes, VAS ratings were performed by 32/61 (52%), 30/62 (48%) and 32/59 (54%) in the non-opioid, codeine and oxycodone groups. The mean VAS reductions from baseline were -18.7 mm, -33.3 mm and -31.7 mm. When recorded, symptom improvement was reported by 17/31 (54.8%), 21/26 (80.0%) and 27/32 (84.4%) respectively.

Of the 182 patients, 104 (57.1%) patients and 97 (53.3%) doctors believed they knew which drugs were administered. The drug regimen was correctly nominated by 49 of 104 (47.1%) patients (kappa 0.11), and 55 of 97 (56.7%) doctors (kappa 0.18).

DISCUSSION

For a convenience sample of adult patients with moderate pain from limb injury, this study found that the non-opioid, codeine and oxycodone groups were all non-inferior to each other, at the primary outcome time of 30 minutes. The effectiveness of each treatment regimen is supported by: the mean VAS reductions for each group exceeding the MCSD of -13 mm; 70% in each group describing symptoms as improved; 80% of patients being satisfied with their treatment; and the need for rescue analgesia being rare.

The most important outcome time could be debated, but with acute pain in the ED setting, our belief is that waiting beyond 30 minutes for some level of pain relief is unreasonable, and studies in the post-operative setting have reported onset of analgesia by 15 minutes.¹² While we did take ratings from the 80% and 52% of patients who remained in the ED at 60 and 90 minutes, the study was neither designed, nor powered, for any firm conclusions to be drawn at these times, as we did not ask patients to remain in the ED for this purpose and had no information on pain severity following ED discharge.

Bearing this in mind, we did find that the 30 minute VAS reductions generally increased further at 60 and 90 minutes, which is consistent with the findings of the two similar ED based trials.⁴⁻⁵ Clark, for moderate pain from limb injury in children, reported similar VAS reductions for codeine, paracetamol and ibuprofen, which progressed from -10 to -15 and -20 mm at 30, 60 and 90 minutes, respectively.⁵ Woo, in adults, reported similar reductions for diclofenac, indomethacin, paracetamol, and one diclofenac + paracetamol combination, which progressed from -5 to -10 and -15 mm at 30, 60 and 120 minutes, respectively.⁴ The VAS reductions of the combination drug regimens in this study generally progressed from -16 to -26 and -32 mm at 30, 60 and 90 minutes. The greater reductions at 30 minutes, in comparison with Clark and Woo, might suggest greater efficacy for combination versus single drug regimens.⁴⁻⁵ Our 90 minute reductions for the codeine and oxycodone groups were also consistent with the findings of Chang, who reported two-hour reductions of -3.5 and -3.9 (0 to 10 numerical rating scale) for combination regimens of paracetamol with either oral hydrocodone or codeine, but this 24-hour follow-up study did not include a non-opioid arm.¹⁵ Our finding for the non-opioid group, that the mean VAS reduction to 90 minutes was

less than it had been at 60 minutes, is not consistent with previous literature,⁴⁻⁵ and is most likely erroneous, confounded by patient loss at this time.

Although not a study of harm, the low side-effect rate in our non-opioid group was consistent with that of Woo,⁴ as was the moderate rate of adverse effects from oxycodone with reports in post-operative patients.¹² The low rate of adverse events in our codeine group is difficult to explain, since other studies report that epigastric discomfort, nausea and drowsiness, occur in 16-20% of adults and children.^{5,6} It is worth noting that codeine use as a regular analgesic has been discouraged in recent years for reasons of low potency in comparison with direct-acting opioids, and poor metabolism in up to 10% of the population.¹⁶ Our findings, and those of Chang, did not support these being significant issues¹⁵. The increasing prescription of opioids is also topical, with particular concerns around their overuse and misuse in the community.¹⁷

LIMITATIONS

We were unable to accurately monitor the number of potentially eligible participants in an ongoing way, or to determine which inclusion or exclusion criteria might have been present in such patients. Our screening suggested that we only recruited about 5 to 6% of eligible patients, and confirmed our anecdotal impression that many patients either presented too long after their injury, or had taken some analgesia prior to assessment in the ED. The reason for the slow enrolment is highlighted by the fact that there was only an average of about one eligible patient at each site per day, which becomes more problematic when busy ED staff is being relied upon for recruitment. This was not anticipated, since we theorised that eligible patients presented more commonly. In retrospect, pilot data would have shown otherwise.

In early 2012, the ongoing slow recruitment precipitated an unplanned change in two of the inclusion criteria, both of which we considered reasonable. The increase in the upper age limit from 65 to 75 years had almost no impact: following the change, only four participants (one non-opioid, one codeine and two oxycodone) were aged 66 to 75 years. The time since injury was increased from eight to 48 hours, to bring the definition in-line with other

literature regarding “acute” injury. This did, as expected, result in an increase in the median time since injury following the alteration, and lead to an increased rate of recruitment. However, there was no significant difference in time since injury across all groups either before or after alteration of the inclusion criterion. The clinical meaning of any non-significant differences in either time since injury or other variables, remains uncertain. Provided that initial pain severity is similar, there is currently no literature to suggest that a person’s response to an analgesic drug is different, depending on whether their injury occurred two or five hours ago, whether they are a twenty-year-old male or forty-year-old female, or whether the trauma is to the wrist or ankle. The sample size of this study did not allow for any such subgroup analyses, but this may be a subject for future research.

On starting the study, the aim was to recruit 72 patients per group. The study was ceased with about 60 patients in each group. Reasons included the expense of replacing all remaining study packs, which had expired at this time, and that the slow recruitment rate and longer study period might risk eventual findings having become obsolete. We believe the generous margin for error we allowed by increasing the probably sufficient sample size of 40 to 72, still allows the results to be meaningful.

Loss of patients by the 60 and 90 minute secondary outcome times meant that VAS reductions and need for rescue medication are not reliable at these times, due to lack of information on those who had left the ED. For this reason, no between-group comparisons were performed at these times. In retrospect, the high early completion of care rates were not surprising, since most limb injuries with only moderate pain are not complex. In addition, at Monash Health, the Diagnostic Imaging target of performing more than 80% of ED imaging requests by 30 minutes is commonly achieved.

Performance bias is another possibility, in that we did not collect information on analgesic adjuncts, such as splints and slings. However, randomisation should ameliorate this potential confounder. Similarly, without a placebo arm, it is not possible to know how much of the pain reduction was unrelated to the medication administered. The lack of identically appearing dummy preparations was also a potential issue. However, the oxycodone,

codeine and thiamine tablets were of similar appearance, consumed without visual inspection, and agreement for both doctors and patients between the suspected and actual drug regimen was poor confirming blinding.

Conclusion

For a convenience sample of adult ED patients with moderate pain from limb injury, this study found that the non-opioid, codeine and oxycodone groups were all non-inferior, at the primary outcome time of 30 minutes. This supports the initial use of a non-opioid combination for moderate pain from limb injury. Duration of adequate analgesic effect, different non-opioid drug and dosage regimens, and effectiveness in other conditions all warrant further investigation.

COMPETING INTERESTS

Andis Graudins is a section editor for EMA in clinical toxicology

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Box 1. Analgesic regimens administered to study subjects: each regimen included six tablets.

Study group	Medication
All	Two x paracetamol 500 mg (Panamax®, Sanofi-Aventis, NSW, Australia)
All	Two x ibuprofen 200 mg (Rafen®, Alphapharm, Victoria, Australia)
Non-opioid	Two x thiamine 100mg (Betamin®, Sanofi-Aventis, NSW, Australia)
Codeine	Two x codeine 30 mg (Codeine Phosphate®, Aspen Pharma, NSW, Australia)
Oxycodone	Two x oxycodone 5 mg (Endone®, Aspen Pharma, NSW, Australia)

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Table 1. Baseline characteristics of patients in each group.

Variable	Non-opioid (n = 61)	Codeine (n = 62)	Oxycodone (n = 59)
Age: median years (IQR) [†]	35 (23 – 46)	31 (22 – 44)	32 (23 – 43)
Males: n (%) [95% CI] [‡]	42 (68.9%) [56.5 – 79.5]	40 (64.5%) [52.1 – 75.7]	44 (74.6%) [62.4 – 84.4]
Time since injury: median minutes (IQR)	180 (60 – 780)	120 (60 – 480)	330 (120 – 1080)
Numerical rating at triage: median (IQR)	6.5 (5 – 7)	7 (5 – 7)	6 (5 – 7)
Enrolment VAS rating: median mm (IQR)	58 (46 – 73)	65 (54 – 73)	56 (40 – 70)
Injury type (n=176)	Upper limb sprain or fracture	25 (41.0%) [28.6 – 54.3]	18 (29.0%) [18.2 – 41.9]
	Upper limb crush or skin wound	5 (8.2%) [2.7 – 18.1]	6 (10.2%) [3.8 – 20.8]
	Lower limb sprain or fracture	28 (45.9%) [33.1 – 59.2]	33 (53.2%) [40.1 – 66.0]
	Lower limb crush or skin wound	3 (4.9%) [1.0 – 13.7]	10 (16.9%) [8.4 – 29.0]

† Interquartile Range

‡ Confidence Interval

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Table 2. Summary of secondary outcomes by group.

Note: Secondary outcomes were reported at the time of the final VAS rating, which may have been at 30, 60 or 90 minutes.

Outcome	Non-opioid	Codeine	Oxycodone
Patient reported satisfaction: n (%) [95% CI] (n at 30/60/90 min)	45/58 (77.6%) [64.7 – 87.5] (n = 12/14/32)	47/58 (81.0%) [67.2 – 89.0] (n = 11/17/30)	39/53 (73.6%) [59.7 – 84.7] (n = 8/14/31)
Additional analgesia: n (%) [95% CI] (n at 30/60/90 min)	11/61 (18.0%) [9.4 – 30.0] (n = 3/3/5)	7/62 (11.3%) [4.7 – 21.9] (n = 0/4/3)	2/59 (3.4%) [0.4 – 11.7] (n = 0/2/0)
Patient reported adverse events: n (%) [95% CI] (type)	2/61 (3.3%) [0.4 – 11.3] -heartburn -lightheaded	1/62 (1.6%) [0.4 – 8.7] -not specified	10/59 (16.9%) [8.4 – 29.0] -4 x lightheaded alone -3 x lightheaded + nausea -2 x nausea alone -1 x drowsy
(n at 30/60/90 min)	(n = 0/0/2)	(n = 0/0/1)	(n = 0/1/9)

† Confidence Interval

Appendix. Patient characteristics and exclusions for those presenting to the ED with mild to moderate pain following limb injury and eligible for enrolment but not recruited to the study.

Total		
13,290 patients (4,771 Casey Hospital, 4,489 Dandenong Hospital, 4,030 Monash Medical Centre) with:		
<ul style="list-style-type: none">- Diagnosis limb fracture/sprain or soft tissue injury- Age 18 to 75 years- Pain rating 4 to 7 out of 10 at any time		
133 (1%) selected for detailed examination		Exclusion
		7 had initial pain rating < 4 or > 7
126		
		34 sustained injury >48 hours prior to presentation
92		
		40 had analgesia in the previous 4 hours
52		
		10 digital injuries
42		
		6 cognitive disorders (5 acute alcohol intoxication, 1 psychosis)
36		
		2 urgent procedures (both clinical shoulder dislocations)
34		Eligible for inclusion (25.5%)
Patient characteristics		Non-recruited subgroup (n = 34)
		Recruited patients (n = 182)
Age: median years (IQR)		24.5 (19 – 33)
Male sex: n (%)		33 (22 – 45)
Triage pain rating: median (IQR)		23 (67.7%)
		126 (69.2%)
		5.5 (4 – 6)
		6 (5 – 7)
Injury type	Upper limb sprain/fracture:n (%)	14 (41.2%)
	Upper limb crush/skin wound: n (%)	65 (35.7%)
	Lower limb sprain/fracture: n (%)	2 (5.9%)
	Lower limb crush/skin wound: n (%)	16 (8.8%)
		16 (47.1%)
		2 (5.9%)
		19 (10.4%)

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EMM_12672_f3.jpg

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Author/s:

Graudins, A;Meek, R;Parkinson, J;Egerton-Warburton, D;Meyer, A

Title:

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