

PREHOSPITAL CARE

Hitting them where it hurts? Low dose nalbuphine therapy

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Objective: To determine if low dose nalbuphine provides an adequate reduction in pain with minimal side effects.

Methods: Prospective cohort of 115 patients given nalbuphine by paramedics in Wales and the English borders.

Outcome measures: (1) Mean total dose of nalbuphine administered, change in pain score, time to adequate pain relief (score below four), and change in respiratory rate and systolic blood pressure; (2) proportion of patients continuing to suffer moderate to severe pain on arrival at hospital; (3) incidence of adverse events.

Results: Full data were obtained for all patients. The mean total dose of nalbuphine administered was 6.09 mg (range 2.5 to 12.5 mg). This was significantly higher in trauma than ischaemic chest pain patients (7.03 versus 5.13 mg). The mean reduction in pain score was -3.97 (95% CI -4.38 to -3.57 , $p < 0.001$). The mean time to adequate pain relief (where this was achieved) was 15.7 minutes (95% CI 13.4 to 17.9 minutes). On arrival at hospital 60% of patients ($n=69$, 95% CI 50.9 to 68.5%) still met ambulance criteria for analgesia (70.7% of trauma patients and 49.1% with ischaemic chest pain). Systolic blood pressure fell by a mean of -3.67 (95% CI -6.76 to -0.58 , $p=0.02$) and respiratory rate increased by a mean of 1.63 (95% CI 1.08 to 2.17, $p < 0.001$). Two patients complained of nausea (1.74%, 95% CI 0.5 to 6.0%). No other adverse events were reported.

Conclusion: Low dose nalbuphine results in few adverse events, but offers poor pain control for a high proportion of patients.

RESEARCH OBJECTIVES

Research question

Does a low dose nalbuphine dosing regimen provide an adequate reduction in pain score with minimal side effects?

Research aims

To determine: (1) the mean total dose of nalbuphine administered; (2) the mean change in pain score; (3) the mean time to adequate pain relief (pain score below four) from the start of the first dose; (4) the proportion of patients continuing to suffer moderate to severe pain on arrival at hospital; (5) the proportion of patients receiving further analgesia after hospital admission; (6) the mean post-nalbuphine change in: (a) respiratory rate; (b) blood pressure; (7) the incidence of adverse events such as nausea, vomiting or dizziness.

BACKGROUND

Nalbuphine hydrochloride (Du Pont Pharmaceuticals Limited, Letchworth Garden City, UK) is a synthetic opioid analgesic agent with agonist-antagonist effects. It has been suggested that nalbuphine is either equipotent with morphine¹⁻³ or has near equipotence.^{4,5} It is recommended for use in moderate to severe pain and its indications include pain after myocardial infarction (manufacturer's data sheet).

Side effects include sedation (most commonly), respiratory depression, sweating, nausea, vomiting, dizziness, dry mouth, vertigo, and headache. Increases or decreases in heart rate and blood pressure have been reported.

Nalbuphine is the only parenteral analgesic currently listed in the Medicines Act permitted for use by NHS paramedics and is therefore used increasingly widely in the prehospital arena. It has been shown to be safe and effective in the prehospital environment when used for the treatment of conditions ranging from burns, multiple trauma, orthopaedic injuries, and intra-abdominal conditions.^{6,7} Nalbuphine has also been shown to be safe and effective as an analgesic after

myocardial infarction.^{8,9} Inappropriate administration by paramedics has, however, also been reported.¹⁰

Nalbuphine has several potential advantages that encourage its use in the prehospital phase of treatment. It is non-controlled and has a low addiction potential, which simplifies its storage and documentation requirements. Respiratory depression, an important side effect of opioid drugs, occurs after administration of nalbuphine to a degree equal to that seen with morphine¹¹ but this has a ceiling effect with increasing doses.^{12,13} Haemodynamic changes, even in patients with cardiac disease, are reported to be minor.¹⁴

Some researchers have voiced concerns about the use of nalbuphine by paramedics, especially the potential for delay at the scene¹⁵ and the possibility of antagonism of other opioids, should further analgesic therapy be required after arrival at hospital.¹⁶ However, other authors have not observed these effects.^{17,18}

Nalbuphine's manufacturers recommend a dosing regimen of 10 mg to 20 mg for a 70 kg patient. In myocardial infarction, they suggest that a dose of 30 mg may be required and that a repeat dose of 20 mg may be given within 30 minutes in the absence of pain relief (manufacturer's data sheet). One investigation examining higher doses in myocardial infarction reported no additional analgesic effect.¹⁹ A further trial, comparing two four-hourly postoperative dosing regimens of 10 mg and 20 mg nalbuphine respectively, found that the lower dose was as effective as the higher but had less unwanted effects.²⁰ It has also been reported that while the systematic clearance of nalbuphine decreases with age, its absolute bioavailability rises and that dosing regimens should therefore be adapted in elderly patients.²¹

One author has reported problems with respiratory depression after utilisation of the manufacturer's recommended dosing regimen by UK paramedics.²² Consequently, when nalbuphine was introduced in our ambulance service, a cautious incremental dosing regimen was implemented (fig 1).

This paper describes the findings of an audit of the first 115 patients to receive nalbuphine after its introduction. Data were

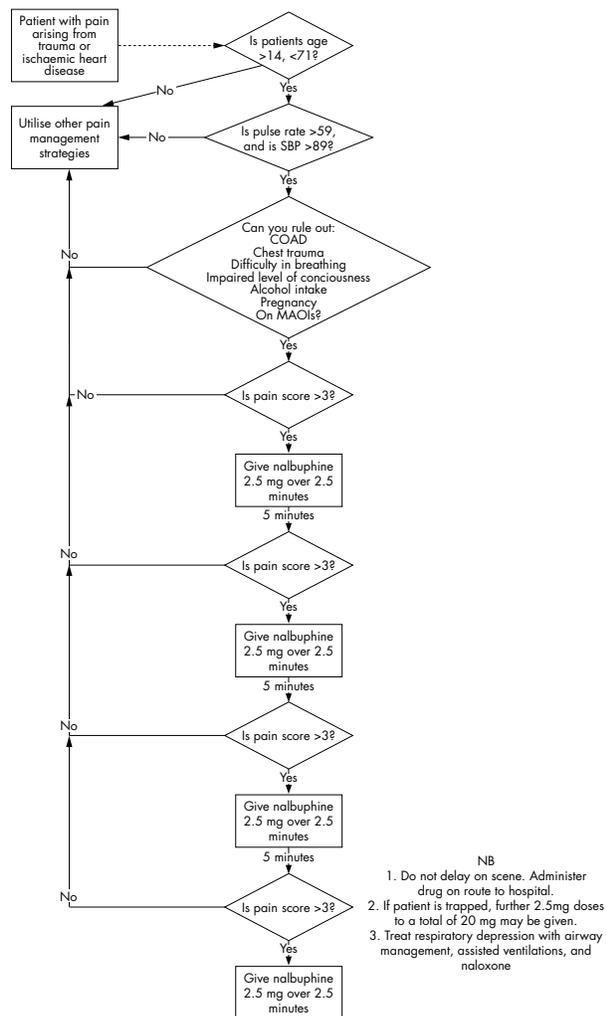


Figure 1 Low dose nalbuphine administration protocol.

gathered from all patients given the drug with the aim of identifying the incidence of side effects such as respiratory depression, changes in blood pressure, and nausea and vomiting. The apparent effectiveness of the drug in relieving pain was also measured using patient-led numerical pain scoring.

METHODS

Inclusion criteria

All patients receiving nalbuphine by our ambulance paramedics in the eight months after its introduction. No patients who received nalbuphine during this period were excluded from the study.

Study design

This prospective cohort study examined data collected routinely from all patients given nalbuphine analgesia by paramedics during the prehospital phase of treatment.

After study of pre-course learning materials and a two hour instructor-led class paramedics were required to achieve an 80% pass mark in an unseen examination. After completion of this certification process our paramedics were authorised by the Local Ambulance Paramedic Steering Committee (LAPSC) to administer nalbuphine to a restricted group of patients.

To facilitate the conduct of a post-implementation clinical audit, a form was designed that provided information supplementary to that routinely collected via the Trust's patient report form.

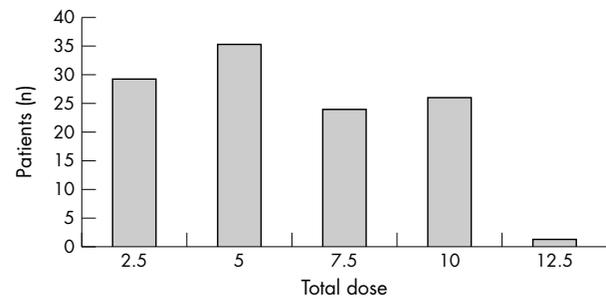


Figure 2 Total dose administered (all patients).

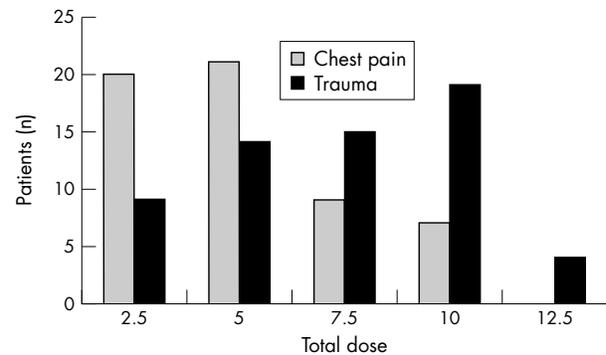


Figure 3 Total dose given (trauma versus chest pain patients).

A literature review was undertaken to determine a suitably objective measure of pain in the prehospital setting, as paramedics had not previously carried out formal assessment. Researchers have suggested that a visual analogue scale (VAS), where the patient is required to mark a 10 cm line to indicate their degree of pain, closely reflects changes in patient's perception of their pain.²³ However, this method is probably impractical in the prehospital setting, particularly when the patient is immobilised to a long spine board or is distressed. The numerical rating scale (NRS) has been shown to correlate well with VAS²⁴⁻²⁶ and has also been recommended for use in a wide variety of settings.²⁷

This scoring assessment of patients' pain was included as a component of the training package. To improve objectivity and reproducibility on the part of paramedics, patients were asked to assign a value between 0 and 10 to their pain, with 0 representing "no pain" and 10 representing "the worst pain possible" (numerical rating scale). A score of four or more was taken to indicate moderate to severe pain, which is the norm for the NRS.

Data were collected from the first 115 patients who received nalbuphine hydrochloride in the eight months after completion of training. Patient report forms were scanned and data read into a patient incident database. Data from the audit forms were entered manually.

Statistical methods

Data were entered into a statistical software package (SPSS, SPSS Inc, Chicago, IL, USA). The Wilcoxin signed ranks test was used to compare mean before and after nalbuphine pain scores, respiratory rate, systolic blood pressure, and mean changes in pain score after nalbuphine administration. The Mann-Whitney U test was used to compare the total doses of nalbuphine administered between groups. The χ^2 test was used to analyse the significance of differences in proportions. Macros written for use with SPSS were used to calculate the 95% confidence intervals for proportions²⁸ and the differences between proportions.²⁹

Table 1 Comparison of efficacy of low doses

	Trauma (% of all trauma patients, 95% CI, n=58)	Ischaemic chest pain (% of all ICP, 95% CI, n=57)	Difference in proportion (95% CI)	p Value for difference
Adequate pain relief with a total dose of 2.5 mg	4 (6.9%, 2.7 to 16.4%)	11 (19.3%, 11.1 to 31.3%)	12.4% (-0.2 to 25.1%)	0.057* (NS)
Adequate pain relief with a total dose of 5 mg	9 (15.5%, 8.4 to 26.9%)	23 (40.4%, 28.6 to 53.3%)	24.8 (8.5 to 39.6%)	0.003

*Fisher's exact test.

Table 2 Change in pain score after nalbuphine administration

	Pre-drug (SD)	Post-drug (SD)	Change (95% CI)	p Value
Pain score (all patients)	8.38 (1.34)	4.41 (2.29)	-3.97 (-4.38 to -3.57)	<0.001
Pain score (chest pain)	8.11 (1.40)	4.12 (2.46)	-3.98 (-4.64 to -3.32)	<0.001
Pain score (trauma)	8.66 (1.22)	4.69 (2.08)	-3.97 (-4.46 to -3.47)	<0.001

Table 3 Comparison of patients with moderate and severe pain states pre-nalbuphine

	Moderate pain (score 4–7) n=28	Severe pain (score 8–10) n=86	p Value for difference
Mean total dose nalbuphine (95% CI) (mg)	5.09 (4.09 to 6.09)	6.42 (5.72 to 7.12)	0.029
Mean pain score pre-nalbuphine (95% CI)	6.71 (6.53 to 6.89)	8.99 (8.81 to 9.17)	<0.001
Mean pain score post-nalbuphine (95% CI)	3.46 (2.85 to 4.07)	4.73 (4.21 to 5.25)	0.026
Mean reduction in pain score post nalbuphine (95% CI)	3.25 (2.55 to 3.95)	4.26 (3.78 to 4.74)	0.019

Table 4 Time to adequate analgesia

Time to adequate pain relief (equivalent dose)	7.5 min (=2.5 mg)	15 min (=5 mg)	22.5 min (=7.5 mg)	>22.5 min (=≥10 mg)
Proportion of patients achieving adequate pain relief (95% CI)	13.0% (8.1 to 20.4)	14.8% (9.4 to 22.4)	8.7% (4.8 to 15.3)	3.5% (1.4 to 8.6)

Informed consent

Our institution's ethical protocols did not require us to obtain informed consent or ethical approval for this study as it used anonymised, routinely collected patient data.

RESULTS

Data from the 115 patients who received nalbuphine were obtained. No patients were excluded from the study. Compliance to completion of audit and patient report forms was high. The only datum missing related to the presence or absence of nausea for one patient. For the purposes of this study "adequate pain relief" was defined as achieving a pain score of less than four (that is, mild to no pain).

Dose

The mean total dose of nalbuphine (for all patients) administered was 6.09 mg (95% CI 5.57 to 6.61 mg, SD 2.81, range 2.5 to 12.5 mg). The chart details the distribution of various doses (fig 2).

Trauma patients (n=58) received a mean total dose of nalbuphine of 7.03mg (95% CI 6.29 to 7.76). Patients with ischaemic chest pain (n=57) received a mean total dose of 5.13 mg (95% CI 4.46 to 5.80 mg). The difference in the mean total doses between trauma and chest pain patients is highly significant (p<0.001) (fig 3).

A 5 mg dose of nalbuphine was significantly more efficacious in the treatment of ischaemic chest pain compared with trauma and was sufficient to provide adequate pain relief

in 40% of patients suffering from this condition. A 2.5 mg dose was adequate in 19.3% of chest pain patients (table 1).

The frequency distributions of the pre-nalbuphine pain scores for both trauma and chest pain patients were very similar (see table 2). It seems, therefore, that the difference in efficacy of nalbuphine at lower doses is not attributable to differences in the degree of pain suffered by chest pain and trauma patients.

Change in pain score after nalbuphine

The reduction in pain score after administration of nalbuphine for all patients is highly significant (table 2).

There is no significant difference, however, in the total reduction in pain score when comparing chest pain and trauma patients.

Comparison of patients with severe and moderate pain

Table 3 compares variables for patients who were scored as having moderate or severe pain before nalbuphine administration. One patient (0.9%, 95% CI 0.2 to 4.8%) received nalbuphine for mild pain, which is outside the protocol (score less than 4) and is therefore not included in this analysis (table 3).

The total dose of nalbuphine, the pre-nalbuphine pain score, the post-nalbuphine pain score, and the mean reduction in pain score were all significantly higher in the group who scored themselves as having severe pain before the administration of analgesia.

Table 5 Need for further analgesia (trauma v ischaemic chest pain patients)

	Condition		Total
	Trauma	Chest pain	
Requirement for further analgesia (as assessed by ambulance paramedics)			
No	17	29	46
Yes	41	28	69
Total	58	57	115

Table 6 Need for further analgesia (ambulance versus hospital staff assessment)

	Further analgesia given in hospital		Total
	No	Yes	
Requirement for further analgesia as assessed by ambulance paramedics			
No	36	10	46
Yes	30	39	69
Total	66	49	115

Time to pain relief

The mean time to adequate pain relief for those patients whose final pain score was below four was 15.7 minutes (95% CI 13.4 to 17.9 minutes). The mean time to last pain assessment for those patients remaining in "moderate" pain was 20.0 minutes (95% CI 17.7 to 22.3 minutes); and was 20.2 minutes (95% CI 14.8 to 25.6 minutes) for those remaining in severe pain. The difference between the mean time to adequate pain relief, and the mean time to the last assessment of pain score in those who did not receive adequate pain relief, is statistically significant ($p=0.007$).

Table 4 stratifies the proportion of patients achieving pain relief within various timescales.

Adequate pain relief (defined as a final pain score of <4) was not achieved for 60% of patients (95% CI 50.9 to 68.5%).

Need for further analgesia on arrival at hospital (as assessed by ambulance staff)

Sixty nine patients (=60%, 95% CI 50.9 to 68.5%) still met the ambulance service's pain score criteria for receiving analgesia on arrival at hospital. Thirteen of these (11% of all patients, 95% CI 7 to 18%) had a final pain score rated as "severe" (>7), and 56 (48.7%, 95% CI 39.8 to 57.7%) continued to suffer moderate pain.

The mean total dose of nalbuphine given to those patients whose final pain score was less than four was 5.22 mg (95% CI 4.47 to 5.97). In those patients assessed by ambulance staff as not achieving adequate analgesia, the mean total dose of nalbuphine administered was 6.67 mg (95% CI 5.98 to 7.36). The difference in the mean doses is highly significant ($p=0.006$) (table 5).

Of the 58 trauma patients, 70.7% (95% CI 58.0 to 80.8%) were assessed as requiring further analgesia by ambulance

staff, compared with 49.1% (95% CI 36.6 to 61.7%) of chest pain patients.

The difference in the proportions of trauma and chest pain patients assessed as requiring further analgesia by ambulance staff is 21.6% (95% CI 3.7 to 37.7%, $\chi^2=5.57$, $p<0.018$).

Differences in perceived need for further analgesia (ambulance versus hospital staff)

Forty nine patients (43% of all patients, 95% CI 34 to 52%) actually received further analgesia after hospital admission (table 6).

There is a statistically significant difference in the proportion of patients assessed as needing further analgesia by ambulance and hospital staff ($\chi^2=13.66$, $p<0.001$).

Ten of the 49 patients receiving further analgesia in hospital (20.4%, 95% CI 11.5 to 33.6%) had a pain score on arrival at hospital of less than four. Thirty of the 69 patients (43.5%, 95% CI 32.4 to 55.2%) who still met Ambulance Trust criteria for nalbuphine on arrival at hospital did not receive further in-hospital analgesia. Clearly the degree of agreement between hospital and ambulance staff assessments can only be described as fair ($\kappa=0.324$).³⁰

Changes in vital signs

Table 7 details mean changes in respiratory rate and systolic blood pressure after nalbuphine administration.

Side effects

Of 115 patients, two reported nausea (1.74%, 95% CI 0.5 to 6.0%). No other side effects or adverse events were reported.

DISCUSSION

Comparatively low total doses of nalbuphine were given. The mean dose given was 6.09 mg, while the drug's manufacturer recommends an initial dose of 10 mg with a maximum dose of 20 mg (30 mg in myocardial infarction).

The mean reduction in pain score was 3.97 on the numerical rating scale. Of concern was the relatively protracted time to achieve adequate pain relief, even in those patients where this did occur. This was achieved within 7.5 minutes in only 13% of patients. This is, at best, unsatisfactory.

Also of concern was the high proportions of patients who either did not achieve adequate pain relief according to the ambulance Trust's pain score criteria (60%), or who required further analgesia in hospital (43%). This difference in proportions seems to be attributable, at least in part, to differences in the assessment of pain between ambulance and hospital staff. Pain scoring is not routinely used in all accident and emergency departments and it has been suggested that both underestimation and overestimation of pain by nursing staff may occur in comparison with a patient-led numerical rating scale.³¹ Consequently, we have based our analysis of the need for further analgesia on the last pain assessment conducted by paramedics for each patient. Regardless of any discrepancy, however, it is clear that adequate pain relief was not achieved for a substantial proportion of patients.

Trauma patients required a significantly higher dose of nalbuphine to achieve a similar reduction in pain score when compared with chest pain patients. Additionally, more trauma patients were assessed as requiring further analgesia. Of those suffering with ischaemic chest pain, a high

Table 7 Changes in patient observations after nalbuphine administration

	Pre-drug (SD)	Post-drug (SD)	Change (95% CI)	p Value
SBP (mm Hg)	138 (25.62)	134 (27.18)	-3.67 [-6.76 to -0.58]	0.02
RR (bpm)	19 (3.76)	20 (5.24)	1.63 (1.08 to 2.17)	<0.001

proportion of patients required a maximum dose of only 5 mg or less to achieve adequate pain relief. This challenges the manufacturer's recommendation for a higher total dose of nalbuphine for ischaemic chest pain (see manufacturer's data sheet).

While the mean changes in systolic blood pressure and respiratory rate after nalbuphine administration reached statistical significance, they resulted in no observed clinical sequelae and are not thought to be of clinical significance. Nausea also seemed to be an infrequent occurrence. It would, therefore, seem evident that a cautious dosing regimen of nalbuphine results in a low incidence of adverse effects. It is unclear if this is attributable to the slow rate of administration of the drug or to the relatively low total doses given.

It seems that while our regimen produces little in the way of adverse events it also results in inadequate pain relief for a large proportion of patients, and in particular those suffering from trauma.

Study limitations

There are a number of variables that we did not attempt to measure precisely and that we have not therefore reported. While our treatment protocol required that paramedics did not increase the time spent on-scene to administer analgesia, we have not studied the effect of the introduction of this protocol on this important parameter. As described elsewhere in this paper the most frequent side effect after nalbuphine administration is sedation, and we did not specifically monitor for this effect. In addition evidence for changes in heart rate was not sought.

We also believe a more detailed analysis of the demography of our patient group would have been of assistance in determining why such a high proportion of patients were assessed as requiring further analgesia on admission to hospital. Consequently it is possible that significant differences (other than whether patients were suffering from trauma or ischaemic chest pain) existed between those requiring further analgesia and those who did not. Systematic differences may have existed in the type and anatomical site of injuries, in age profiles, or in journey times to hospital (short journey times preventing administration of the maximum dose of analgesic). Importantly, while there was a significant difference in the proportions of trauma and chest pain patients requiring further analgesia, this could also be attributable to a hidden confounding effect of a difference in journey times.

In conclusion, following this cohort study it is apparent that the initial dose of nalbuphine should be increased to provide adequate analgesia rapidly for a greater proportion of patients. Based on our study data, if the initial dose is increased to 5 mg this will more than double the number of patients achieving adequate pain relief within 7.5 minutes.

The incremental doses of nalbuphine should also be increased to 5 mg. The interval from the start of one dose to the start of a subsequent dose should be reduced to five minutes (that is, give 5 mg over two minutes and re-assess pain after a further three minutes). This should result in all of the "in pain" patients for whom nalbuphine is likely to have an effect (based on our data) achieving adequate pain relief within 15 minutes. But it should be emphasised that this may increase the incidence of adverse effects, particularly if this is related to the speed of administration of the drug as well as to the dose given.

It is also recommended that the maximum dose of nalbuphine be increased to 20 mg in all circumstances where administration of a parenteral analgesic is appropriate. This, coupled with speeding the rate of drug administration, will assist in increasing the total number of patients who receive adequate pain relief before arrival at hospital. Again, caution must be exercised in that this may increase the incidence of adverse events.

There is a need to standardise the assessment of patient's need for analgesia between ambulance and hospital staff. We recommend that accident and emergency department personnel adopt the numerical rating scale as an objective and easily applied assessment tool.

Other areas of the UK use various dosing regimens for nalbuphine hydrochloride. For example, in a different area of Wales, the regimen provides for an initial dose of 10 mg given over 30 seconds, with a further 20 mg if no relief is noted within the next three minutes. The authors of this paper are unaware of any randomised controlled trial that has been undertaken to compare the effects of these various regimens on pain relief and physiological variables. Further research is required to determine the optimum nalbuphine regimen that provides adequate pain relief with minimal side effects. In particular this should seek to determine if the incidence of side effects rises with either higher doses or more rapid administration. It should also include an assessment of the need for different dosing regimens for trauma and ischaemic chest pain patients.

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Contributors

Malcolm Woollard conceived the idea for the paper, wrote the first draft, and analysed the data. Tim Jones conceived the idea for the research, collected the data, and edited the paper. Karen Pitt assisted in the analysis of the data and edited the paper. Norman Vetter assisted in the analysis of the data and edited the paper.

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REFERENCES

- 1 **Zacny JP**, Conley K, Marks S. Comparing the subjective, psychomotor and physiological effects of intravenous nalbuphine and morphine in healthy volunteers. *J Pharmacol Exp Ther* 1997;**280**:1159-69.
- 2 **Miller RR**. Evaluation of nalbuphine hydrochloride. *American Journal of Hospital Pharmacy* 1980;**37**:942-9.
- 3 **Errick JK**, Heel RC. Nalbuphine. A preliminary review of its pharmacological properties and therapeutic efficacy. *Drugs* 1983;**26**:191-211.
- 4 **Beaver WT**, Feise GA. A comparison of the analgesic effect of intra-muscular nalbuphine and morphine in patients with post-operative pain. *J Pharmacol Exp Ther* 1978;**204**:487-96.
- 5 **Lee JJ**, Marvin JA, Heimbach DM. Effectiveness of nalbuphine for relief of burn debridement pain. *J Burn Care Rehabil* 1989;**10**:241-6.
- 6 **Stene JK**, Stofberg L, MacDonald G, et al. Nalbuphine analgesia in the pre-hospital setting. *Am J Emerg Med* 1988;**6**:634-9.
- 7 **Chambers JA**, Guly HR. Prehospital intravenous nalbuphine administered by paramedics. *Resuscitation* 1994;**27**:153-8.
- 8 **Jamidar HA**, Crooks SW, Adgey AA. Nalbuphine versus diamorphine early in the course of suspected myocardial infarction. *Eu Heart J* 1987;**8**:597-602.
- 9 **Nikoda VV**, Lebedeva RN, Artamoshina, MP, et al. Comparative evaluation of the use of nalbuphine and buprenorphine in prehospital care. *Anesteziol Reanimatol* 1998;**5**:23-8.
- 10 **Gray A**, Johnson G, Goodacre S. Paramedic use of nalbuphine in major injury. *Eur J Emerg Med* 1997;**4**:136-9.
- 11 **Gal TJ**, DiFazio CA, Moscicki J. Analgesic and respiratory depressant activity of nalbuphine: a comparison with morphine. *Anesthesiology* 1982;**57**:367-74.
- 12 **Klepper ID**, Rosen M, Vickers MD, et al. Respiratory function following nalbuphine and morphine in anaesthetized man. *Br J Anaesth* 1986;**58**:625-9.
- 13 **Romagnoli A**, Keats AS. Ceiling effect for respiratory depression by nalbuphine. *Clin Pharmacol Ther* 1980;**27**:478-85.
- 14 **Lake CL**, Duckworth EN, DiFazio CA, et al. Cardiovascular effects of nalbuphine in patients with coronary or valvular heart disease. *Anesthesiology* 1982;**57**:498-503.

- 15 **Johnson GS**, Guly HR. The effect of pre-hospital administration of intravenous nalbuphine on on-scene times. *J Accid Emerg Med* 1995;**12**:20–2.
- 16 **Houlihan KP**, Mitchell RG, Flapan AD, et al. Excessive morphine requirements after pre-hospital nalbuphine analgesia. *J Accid Emerg Med* 1999;**16**:29–31.
- 17 **Bailey PL**, Clark NJ, Pace NL, et al. Failure of nalbuphine to antagonize morphine: a double-blind comparison with naloxone. *Anesth Analg* 1986;**65**:605–11.
- 18 **Kelly AS**, Guly HR. Nalbuphine - the optimal pre-hospital analgesic for lower limb fractures? *Pre-hospital Immediate Care* 1999;**3**:224–5.
- 19 **Trouton TG**, Adgey AA. High dose nalbuphine in early acute myocardial infarction. *Int J Cardiol* 1989;**23**:53–7.
- 20 **Bagilet D**, Desposito J, Giovannoni A, et al. Nalbuphine. Comparison of two therapeutic regimens for the control of postoperative pain. *Medicina (B Aires)* 1993;**53**:503–6.
- 21 **Jaillon P**, Gardin ME, Lecocq B, et al. Pharmacokinetics of nalbuphine in infants, young healthy volunteers, and elderly patients. *Clin Pharmacol Ther* 1989;**46**:226–33.
- 22 **Dempsey C**. Nubain audit. *Ambulance UK* 1996;**11**:6–7.
- 23 **Ohnhaus EE**, Adler R. Methodological problems in the measurement of pain: a comparison between the verbal rating scale and the visual analogue scale. *Pain* 1975;**1**:379–84.
- 24 **Price DD**, Bush FM, Long S, et al. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. *Pain* 1994;**56**:217–26.
- 25 **Ekblom A**, Hansson P. Pain intensity measurements in patients with acute pain receiving afferent stimulation. *J Neurol Neurosurg Psychiatry* 1988;**51**:481–6.
- 26 **Seymour RA**. The use of pain scales in assessing the efficacy of analgesics in post-operative dental pain. *Eur J Clin Pharmacol* 1982;**23**:441–4.
- 27 **Bolton JE**, Wilkinson RC. Responsiveness of pain scales: a comparison of three pain intensity measures in chiropractic patients. *J Manipulative Physiol Ther* 1998;**21**:1–17.
- 28 **Wilson EB**. Probable inference, the law of succession, and statistical inference. *Journal of the American Statistical Association* 1927;**22**:209–12.
- 29 **Newcombe RG**. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med* 1998;**17**:873–90.
- 30 **Altman DG**. *Practical statistics for medical research*. London: Chapman and Hall, 1991:404–5.
- 31 **Bondestam E**, Hovgren K, Gaston JF, et al. Pain assessment by patients and nurses in the early phase of acute myocardial infarction. *J Adv Nurs* 1987;**12**:677–82.