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.
paramedics during the prehospital phase of treatment. This prospective cohort study examined data collected routinely from all patients given nalbuphine analgesia by our ambulance paramedics in the eight months after its introduction. No patients who received nalbuphine during this period were excluded from the study.

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.

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. 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 VAS and has also been recommended for use in a wide variety of settings.

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 worse 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 Wilcoxon 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 $\chi^2$ 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 proportions and the differences between proportions.

Figure 1 Low dose nalbuphine administration protocol.

Figure 2 Total dose administered (all patients).

Figure 3 Total dose given (trauma versus chest pain patients).
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 an average total dose of 7.03 mg (95% CI 6.29 to 7.76). Patients with ischaemic chest pain (n=57) received an average 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.
is statistically significant (p=0.007).

The mean time to the last assessment for those patients remaining in severe pain. The difference between 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 paramedics)**

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 who 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.

**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.

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 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 (\( \kappa=0.324 \)).

**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.

**Table 7** Changes in patient observations after nalbuphine administration

<table>
<thead>
<tr>
<th></th>
<th>Pre-drug (SD)</th>
<th>Post-drug (SD)</th>
<th>Change (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>138 (25.62)</td>
<td>134 (27.18)</td>
<td>-3.67 [-6.76 to -0.58]</td>
<td>0.02</td>
</tr>
<tr>
<td>RR (bpm)</td>
<td>19 (3.76)</td>
<td>20 (5.24)</td>
<td>1.63 (1.08 to 2.17)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

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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 analgesia). 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 regimes 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 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 Woolard 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**


