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Nose and vein, speed and pain: comparing the use of intranasal diamorphine and intravenous morphine in a Scottish paediatric emergency department

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ABSTRACT

Background Urgent analgesia is essential for all children who present in severe pain, but difficulties in obtaining venous access can delay the use of adequate opiate analgesia. Intranasal diamorphine (IND) is now in use in around 60% of emergency departments and is the preferred choice of analgesia as reported by both parents and healthcare professionals. While IND has similar efficacy to intramuscular morphine in children, no study has compared its use against the current gold standard, intravenous morphine (IVM).

Methods IND was introduced to the Royal Aberdeen Children's Hospital on 24 December 2009. A retrospective case series was constructed to compare its clinical performance with its predecessor IVM. Three unexplored factors were investigated: time to opiate analgesia, the requirement for further analgesia when still in the emergency department and the effect of simple coanalgesia (eg, paracetamol/ibuprofen) on these requirements.

Results 297 patients were eligible for the study (147 IND, 150 IVM) over a 28-month period. There was a non-significant trend to a longer median time to administration of analgesia in patients receiving IND ($p=0.170$). Patients who received IND were less likely to require further analgesia ($p<0.001$). Both groups were less likely to require further analgesia when simple coanalgesia was given ($p=0.049$).

Conclusion The authors found no significant difference in time to administration of analgesia between agents, but a learning curve has been identified. Sustained effort should be placed on the use of simple coanalgesia. The clinical performance of IND compares favourably with IVM in children with severe pain, and it remains an appropriate preferred agent.

BACKGROUND

Urgent opiate analgesia is essential for all children who present in severe pain, but the debate remains as to the most appropriate first route of administration. Difficulties in obtaining venous access can increase levels of distress for already traumatised children, as well as introducing a delay in the use of adequate opiate analgesia. As the only indications for venous cannulation are fluid resuscitation or emergency anaesthesia, other approaches should be considered. Intramuscular administration of morphine is no longer routinely recommended in children, and due to the limited efficacy of oramorph preparations and problems of delayed gastric emptying, additional, rapid and reliable routes of administration are necessary.[1]

Intranasal diamorphine (IND) is used as an off-licence preparation by around 60% of paediatric emergency departments in England and Wales,[2 3] and is the preferred choice of opiate analgesia as reported by both parents and healthcare professionals.[2 4–6] Indeed, IND now features within the College of Emergency Medicine's framework for managing severe pain in children.[7] This application harnesses the rich vascular bed of the nasal mucosa, which drains through fenestrated epithelium and via the facial and sphenopalatine veins, thereby avoiding first pass metabolism. The lipophilic and highly soluble properties of diamorphine hydrochloride enable its use as an intranasal preparation: high concentrations of drug are delivered in small volumes (0.1 ml) of saline, thus promoting maximal absorption.[8]

IND has an excellent safety profile[1 2 4 6 8–15] and greater efficacy than intramuscular morphine in children.[5 6] Mitchell *et al*[11] examined the performance of IND as a replacement for intravenous diamorphine maintenance therapy in opiate abusers, and concluded that it was an attractive alternative with similar efficacy. However, Ward *et al*[12] studied its use in the postoperative setting for patient controlled analgesia, suggesting that in this subgroup of patients, intravenous diamorphine was the ideal preparation. While these studies provide useful information on safety and efficacy, they are of little practical clinical use when evaluating IND for severe pain in children.

Kidd *et al* compared the pharmacokinetic aspects of IND with intravenous diamorphine in children[16] and showed an attenuated peak plasma concentration compared with intravenous diamorphine, the clinical significance of which is not known. At the time of writing, there is no clinical evidence comparing IND against the current gold standard for severe pain in children, intravenous morphine (IVM).

This study compares the clinical performance of IND with IVM over three previously unexplored factors which are of paramount importance when giving analgesia in severe pain: the time delay in drug administration, its efficacy (both with and without coanalgesic agents such as paracetamol or ibuprofen) and the requirement for further analgesia when still in the emergency department.

PARTICIPANTS AND METHODS

A retrospective consecutive case series was constructed to include all patients who received treatment with IND from its introduction on 24

December 2009 to 17 October 2010 in the paediatric emergency department of the Royal Aberdeen Children's Hospital. Patients were identified from prescription records taken from the controlled drugs register. A second cohort was then obtained in a similar manner, beginning on 23 December 2009 and progressing retrospectively to include a comparable number of patients treated with IVM.

In clinical practice, children are identified as requiring analgesia for severe pain by either the nursing or medical staff using pain scoring or visual analogue scales as appropriate, and any relative contra-indications (such as coexisting respiratory or central nervous system (CNS) depression) identified. Either a single dose of 0.1 mg/kg IND or a 0.1 mg/kg bolus of IVM over 5 min is given, with SpO_2 and CNS observations monitored. Any complications such as vomiting, reduced level of consciousness or requirement for naloxone are recorded.

Data collection

All available patient records were accessed and basic demographical data obtained to ensure both cohorts were comparable. Case notes were then reviewed for time of arrival, time of administration of opiate analgesia, the presence of any complications, usage of simple coanalgesia and requirement for further analgesia when in the department. Cases were excluded if analgesia was given immediately prior to a painful procedure. No identifiable patient data were collected, and data were collated in SPSS V.18.1.

Statistical analysis

The sample size was dictated by the number of children treated over a 10-month period, and the comparative cohort sought to identify a similar number of children. Time to opiate analgesia was compared using the Mann–Whitney U test while differences in demographics, rates of simple coanalgesia and rates of further analgesia were compared using the χ^2 test of association. Analysis was conducted using SPSS V.18.1, with $p<0.05$ taken as significant.

RESULTS

Population

Three hundred and sixty-four patients were identified from the controlled drugs register (179 IND, 185 IVM), with 302 cases available for review due to missing records (150 IND, 152 IVM). When exclusion criteria were applied, a total study population of 297 was available (147 IND, 150 IVM). This process is summarised in figure 1. Both cohorts were well matched with no differences in age ($p=0.331$) or gender ($p=0.544$) as shown in table 1.

Complications

No serious side effects such as respiratory or CNS depression was noted in either cohort, and the administration of naloxone was not required at any point. Two patients within the IVM cohort required antiemetics for vomiting (1.3%); however, no patients in the IND cohort required an antiemetic.

Rate of prescription

While 179 patients received IND within the first 10 months of its introduction to the paediatric emergency department, the morphine dataset had to extend over 17 months to obtain a comparable number of subjects. IND was prescribed to an average of 18 patients per month whereas IVM was prescribed to an average of 11 patients per month.

Time to opiate analgesia

The median time to opiate analgesia was found to be longer in patients receiving IND compared with IVM; yet, this difference was not statistically significant, as shown in table 1. The College of Emergency Medicine standard of analgesia for children in severe pain within 20 min was not met, with a median time of 30 min for nasal diamorphine administration and 25.5 min for morphine. During the first 5 months, the median time to nasal diamorphine was 37 min; however, this reduced to 25 min in the second period suggesting a learning curve. This is detailed in figure 2.

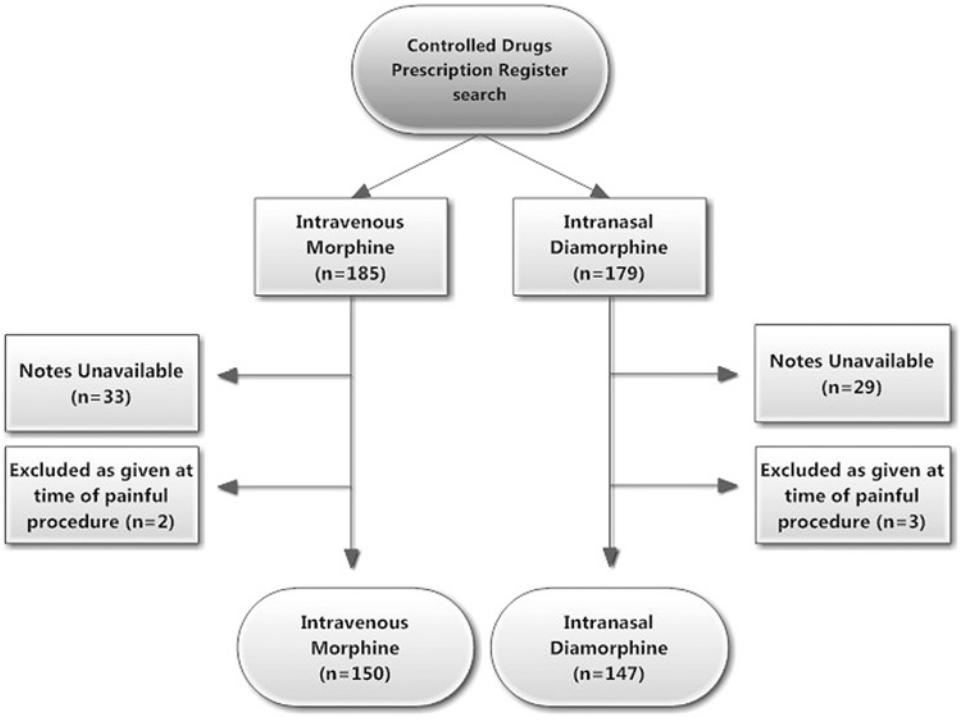

Figure 1 Flow diagram summarising the identification of patients to form both cohorts.

Table 1 Key demographics and time to opiate analgesia comparison between cohorts

	Intranasal diamorphine	Intravenous morphine	Comparison
Age±SD (range)	7.2±3.6 (3 months–13 years)	6.9±3.3 (2 months–12 years)	p=0.331*
Gender	Male—99	Male—96	p=0.544*
	Female—44	Female—54	
Time to administration of analgesia (min)	Median 30	Median 25.5	p=0.170†
	Mean 43.9	Mean 39.4	
	95% CI 40.9 to 47.0	95% CI 33.2 to 45.6	
	Range (2–177)	Range (2–260)	

*χ^2 test of association.
†Independent samples Mann–Whitney U test.

Simple coanalgesia and further analgesia

There was no difference between groups with regard to rates of coanalgesia prescription (p=0.244). Patients who received IND were significantly less likely to require further analgesia than those who received IVM (p<0.001). Patients in both the IND and IVM cohorts were significantly less likely to require further analgesia if initial simple coanalgesia was given (p=0.049), as shown in figure 3.

DISCUSSION

The initial target of 150 patients in the IVM comparison cohort was met, and demographic data suggest valid comparisons between the cohorts can be made. There were no recorded instances of opiate toxicity or naloxone use, and extremely low rate of complications confirm that these drugs are used safely and tolerated well by children in severe pain.

One of the obvious advantages of IND is the lack of a requirement for venous access. It follows therefore that one would anticipate the time to administration of analgesia would be shorter in this group. However, the median time to administration was in fact marginally longer. While this was a non-significant result, it does merit discussion.

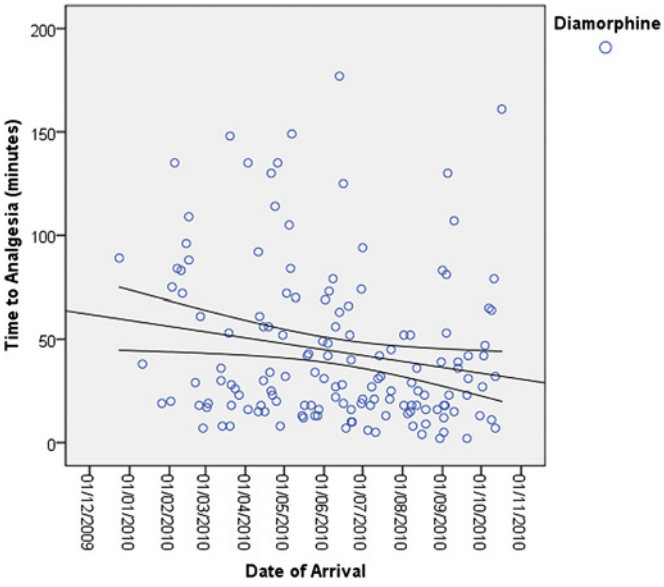

Figure 2 Scatterplot displaying time to analgesia dated from the introduction of intranasal diamorphine to the emergency department, with linear best fit and 95% CIs shown.

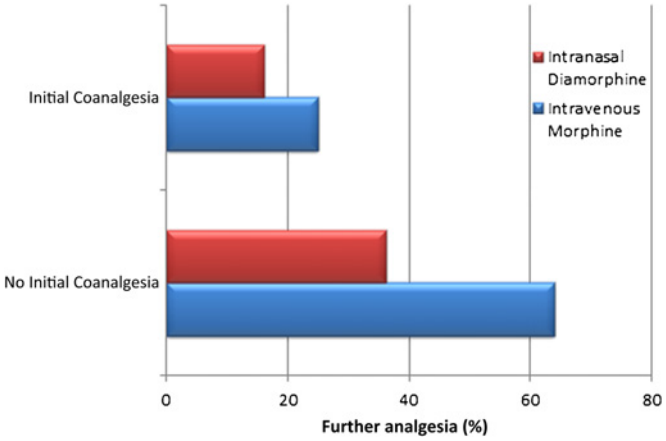

Figure 3 Rates of further analgesia compared with initial coanalgesia in both morphine and diamorphine cohorts.

A number of children who present to the emergency department will already have venous access established by paramedics, and their time to opiate analgesia would be expected to be reduced. Furthermore, as figure 2 highlights, time to administration analgesia has declined since the introduction of IND. It is likely that a technical learning curve has been found, and as staff become more familiar with the use of nasal diamorphine we are optimistic that a repeat study will show an improved time to administration of analgesia.

The College of Emergency Medicine standard for children in moderate to severe pain states that all children should receive initial analgesia within 20 min, and this should be re-evaluated within 60 min.[7] The department narrowly failed to achieve this standard, with median times to analgesia of 30 min for IND and 25.5 min for IVM. Further information has been disseminated to staff as a result of this work and we hope to observe improvements in future.

IND was prescribed at an increased monthly frequency compared with IVM. It is possible that due to its ease of use, lack of requirement for venous access and staff confidence with the use of nasal diamorphine, the stigma of opiate use has been lifted somewhat. Given qualitative survey evidence which is already published, this explanation seems likely.[4 6 13]

Rates of further analgesia prescription in the IND group were significantly lower than those of the IVM group (p<0.001). Upon further analysis, it became apparent that the initial bolus of IVM was often followed by subsequent doses titrated to effect. It is possible that this is due to a reluctance of staff to administer a more adequate initial intravenous bolus for fear of precipitating opiate toxicity. As the initial bolus could not be calculated for all children studied we cannot confirm this postulation with absolute certainty, but it certainly warrants consideration.

As the nasal route of administration of diamorphine is an indirect route to the systemic circulation and is known to take longer to establish a peak plasma concentration of active metabolite than intravenous administration of morphine, it is possible that staff may be less intimidated by its use. This may also have resulted in an increased rate of prescription of opiate analgesia via the nasal route (compared with the historical cohort) by staff keen to minimise pain in children who may otherwise have received alternative, less efficacious oral analgesia in the past.

Rates of coanalgesia prescription were found to be similar in both groups of the study with no statistical differences observed.

Those prescribed coanalgesia were however significantly less likely to require further analgesia when in the department, and this trend was noted in both groups. It is important therefore not to underestimate the effectiveness of adjuvant simple analgesia when administering opiate medication, and efforts should be made to ensure patients receive some form of non-opiate coanalgesia where possible.

This is the first study to compare the clinical performance of IND with the gold standard of IVM. Despite being a single centre study, our department represents a typical paediatric emergency setting with a high turnover of patients, and our results are likely to be generalisable.

The primary weakness of this study remains the significant percentage of patient notes that were unavailable for analysis; however, given our total population of 300 patients, our results are likely to be representative.

The absence of a 'cause of pain' within our dataset could potentially confound the children's requirements for further analgesia over time. However, given the relatively large sizes of both groups and their consecutive enrolment, neither cohort should be unfairly biased.

While this retrospective series is not without its limitations, it may be difficult to justify a randomised controlled trial at this stage. There is a demand for more research in this area, but it has been shown that nasal diamorphine is non-inferior to intravenous diamorphine in adults,[12] and as both parent and staff satisfaction with IND is high,[4 6 13] ethical approval may prove difficult to obtain in a paediatric population.

CONCLUSIONS

Perhaps surprisingly, we found no significant difference in time to administration of analgesia between IND and IVM at present; however, a learning curve has been identified. As IND has been prescribed at a much greater monthly rate than its predecessor, it appears that emergency physicians are less reluctant to use this method of analgesia.

Our results may suggest that IND is a more effective analgesic agent as lower prescription rates of further analgesia have been observed, but this finding must be interpreted with caution. It seems likely that the initial bolus of IVM has been inadequate on occasion, and subsequent doses are therefore required. Given pharmacokinetic data available already this is unlikely to be a true demonstration of increased efficacy.

Of significance, we note the near halving of further analgesic requirements for all patients when simple coanalgesia was prescribed. We suggest sustained emphasis should be placed on prescribing some form of non-opiate coanalgesia to all children at presentation. The clinical performance of IND, specifically, the time to administration of analgesia and the need for further analgesia, compares favourably with IVM in children with severe pain, and it remains an appropriate first choice for initial pain relief.

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Contributors LR: concept, data analysis, article preparation. ARC: data collection, data analysis, article preparation. AC: data collection, data analysis. LL, RA-S and NPM: data collection.

Competing interests None.

Ethics approval This project is a retrospective consecutive case series, auditing the management of pain relief in children using two different methods of analgesia—as such, no formal ethical approval was required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Raw data are available on request alongside evidence of statistical analysis.

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Notes