Multicentre randomised controlled trial of nasal diamorphine for analgesia in children and teenagers with clinical features

Kendall JM, Reeves BD, Latter VS

BMJ (2001) 322 , 261 - 265

Was the assignment of subject to treatments randomised?

Yes. They used concealed codes and, to ensure similar numbers in the randomisation in the different centres they used a block randomisation with different sized blocks so that it was not possible to recognise that there was a sequence of patterns. The difficulty of recruiting people in an A&E department is alluded to but they do not mention any attempt to recruit consecutive patients at times when staff were plentiful and there is sufficient opportunity for selection of patients, especially as they do not define 'major delay' in offering pain relief. No information is given about how many patients were recruited in each hospital, nor how long the study went on for.

Was the potential assignment concealed?

Yes. The patients who were randomised had previously met inclusion and exclusion criteria and had been consented.

Were all the subjects who entered the trial properly accounted for and attributed at its conclusion?
Was follow-up complete?

Figure 1 implies that they have outcome data on 408/413 but table 2 shows that individuals are missing throughout and, while there may be at least one outcome measure on all, individuals are missing from all time points.

Did the authors justify their use of follow-up time?

Follow-up was 30 minutes and there was no justification given for the use of this time. Logistically a longer time may prove difficult.

Were subjects, researchers and healthcare personnel 'blind' to the intervention or treatment?

No. This is a comparison of a nasal spray and an i-m injection. They considered it unethical to give dummy injections – so was it ethical to give injections to half the group? They also justified the lack of blinding by saying they wanted to assess the acceptability of the two procedures but that had already been answered by their statement about the ethics, and, anyway, does that particular question need answering, or are there others that would be more useful?

Were the subjects similar at the start of the trial?

Table 1 gives that information and they seem comparable.

Aside from the intervention, were the subject groups treated equally?

Probably. Patients were offered rescue analgesia (the control therapy) which was taken up equally by each group. The comparability of the two preparations at the doses in which they have been used is defended and references provided.

Were data from the groups analysed according to randomisation? – i.e. intention to treat analysis?

They said yes but figure 1 shows that they excluded 6 from the control group (3 of whom should not have reached randomisation) and another 3 from the active treatment group.

Effect of intervention.
What is the difference in measured outcome(s) between the groups?

The main outcome was pain score as assessed by patient recording of the Wong Baker face pain scale (an ordered 6 face scale). The study had used this, or a visual analogue scale, or both, but only the Wong Baker scale was used because very young children couldn't use the visual scale. Some of those children would not, therefore, have been offered access to the Wong Baker scale. From the numbers reporting an outcome in Table 2 the missing must have been small – of the order of 10.

The change in pain score was assessed using a Chi-square test for trend. This assesses whether there is a difference in the proportion of responses in each of the pain faces between the two groups, and whether that difference is an ordered one (trend). In other words, was the movement down to a lower pain group faster in one group compared with the other? Pain assessment before treatment was similar, with significant differences being seen between 5 and 20 mins, but not at 30 mins. Figure 2 is not very helpful as it reports cumulative responses. Table 2 shows that, after 5 minutes and 10 minutes, proportionately fewer children in the nasal spray group appear to be represented in the worst pain group. At 10 and 20 minutes there appear to be more children in the low pain groups, 1 and 2, if they have had nasal spray.

Responses from carers and staff are not shown but said to be similar.

Other outcomes assessed were nurse recording of reaction to administration, nurse, patient and carer recording of treatment acceptability, staff recording of adverse event intensity and some physiological measures. They talk about oxygen saturation being slightly lower at 5, 10 and 30 minutes, provide no data and don't say whether or not it is significant, yet use this to help justify the pain relief results. Unsurprisingly nasal spray was seen to be more acceptable and less painful than an injection. What should be considered here is whether the control used is the appropriate control for this group, or should the comparison be being made between nasal spray and an oral solution? Although authors argue problems with drug choice and delayed gastric emptying for oral solutions, their report is anecdotal only.

How likely is this to be due to chance?

The p-value tells you about chance. The difference seen at 20 minutes is likely to be seen only about 1 in 500 times (p=0.002) if there is really not difference in the trend to a faster move to a lower pain level.

Is a confidence interval quoted for the intervention?

Differences in proportions are generally reported along with a confidence interval. For example 35% more patients would be happy to have nasal spray again than have the I-m injection. The confidence interval on this difference was from 28% to 43%.

What does this imply?

It is likely that at least 29% more people would be happy to have the nasal spray again, compared with the i-m injection, and this difference could be as great as 43%.

Does this paper justify the likely benefits as worth the potential harms and costs (if any)?

No. Benefits are not justified since the control group seems inappropriate and probably unethical. Why did they not try oral morphine? The difference in pain score is not large, and is only evident up to 20 minutes. There was no significant difference in non-serious (not

defined) adverse events, although they were more common in the spray group. The confidence interval on this difference suggests a possible lack of power. They appear to have done a retrospective power calculation to exclude a 'serious rate for an adverse event' – or do they mean 'rate for a serious adverse event'? – and need 200 per group to exclude 18 events in 1000. They say, but do not provide any more information, that this number is sufficient to detect a clinically important difference in pain score. For example, what is a clinically importance difference, and what is ample power? Again they do not define these. It also hardly needs a study to declare that a nasal spray would be preferred to having a needle stuck in you, which is the only really significant outcome.

It is possible to back calculate using the statistics they provide. If we assume that we are looking to be able to detect an adverse rate of 1.8% with a statistical probability of 0.05 or less and that we plan to have 200 in each group then the power is calculated at about 48%. That means that there is only about a 50% chance of detecting such a difference. I would not call that ample. If we were to require 90% power then we would need just under 600 in each group, reducing to just over 400 in each group for 80% power. It could be that they have just misinterpreted the latter as needing 400 people in total – 200 per group. Given other things in the paper this would not seem too unlikely.

It should be noted when valuing the results of this study that the Nasal Diamorphine Trial Group compose an A&E consultant from Bristol, the director of the Clinical Effectiveness Units at the RCS, and the manager of UCL's Clinical Research Network. At the end of the paper we note that CP Pharmaceuticals provided the drugs and analysis. One of the authors received a fee for 'cleaning and analysis' but paid into a research fund and another author worked for CP during the study. It is not stated whether or not this company manufactures anything utilised in this study.