

Respiratory and haemodynamic effects of acute postoperative pain management: evidence from published data

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Background. This study examines the evidence from published data concerning the adverse respiratory and haemodynamic effects of three analgesic techniques after major surgery; i.m. analgesia, patient-controlled analgesia (PCA), and epidural analgesia.

Methods. A MEDLINE search of the literature was conducted for publications concerned with the management of postoperative pain. Information relating to variables indicative of respiratory depression and of hypotension was extracted from these studies. Over 800 original papers and reviews were identified. Of these papers, 212 fulfilled the inclusion criteria but only 165 provided usable data on adverse effects. Pooled data obtained from these studies, which represent the experience of a total of nearly 20 000 patients, form the basis of this study.

Results. There was considerable variability between studies in the criteria used for defining respiratory depression and hypotension. The overall mean (95% CI) incidence of respiratory depression of the three analgesic techniques was: 0.3 (0.1–1.3)% using requirement for naloxone as an indicator; 1.1 (0.7–1.7)% using hypoventilation as an indicator; 3.3 (1.4–7.6)% using hypercarbia as an indicator; and 17.0 (10.2–26.9)% using oxygen desaturation as an indicator. For i.m. analgesia, the mean (95% CI) reported incidence of respiratory depression varied between 0.8 (0.2–2.5) and 37.0 (22.6–45.9)% using hypoventilation and oxygen desaturation, respectively, as indicators. For PCA, the mean (95% CI) reported incidence of respiratory depression varied between 1.2 (0.7–1.9) and 11.5 (5.6–22.0)%, using hypoventilation and oxygen desaturation, respectively, as indicators. For epidural analgesia, the mean (95% CI) reported incidence of respiratory depression varied between 1.1 (0.6–1.9) and 15.1 (5.6–34.8)%, using hypoventilation and oxygen desaturation, respectively, as indicators. The mean (95% CI) reported incidence of hypotension for i.m. analgesia was 3.8 (1.9–7.5)%, for PCA 0.4 (0.1–1.9)%, and for epidural analgesia 5.6 (3.0–10.2)%. Whereas the incidence of respiratory depression decreased over the period 1980–99, the incidence of hypotension did not.

Conclusions. Assuming a mixture of analgesic techniques, Acute Pain Services should expect an incidence of respiratory depression, as defined by a low ventilatory frequency, of less than 1%, and an incidence of hypotension related to analgesic technique of less than 5%.

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In a previous publication, we referred to the 1997 Audit Commission report, and its recommendation that by 2002 less than 5% of patients should experience severe pain after surgery.¹ In that study, we suggested that pain and pain relief were only part of the many outcome variables with which Acute Pain Services should be interested. We proposed that the safety and tolerability of the analgesic

techniques used were also important aspects to be considered. Furthermore, we suggested that the incidence of respiratory depression and hypotension might be indicative of the safety of a technique. The occurrence of nausea and vomiting, sedation, itching or the need for urinary catheterization might be considered to be indicative of the tolerability of a technique.

In this, the second of three studies, we have examined the evidence from published data with regard to adverse respiratory and haemodynamic effects of i.m., patient controlled and epidural analgesic techniques. In particular, we have examined the three analgesic techniques with respect to the incidence of respiratory depression and hypotension after major surgery.

Methods

Search strategy

Full details of the search strategy and methodology have been described in a previous publication.¹ We carried out a MEDLINE search (1966 onwards) of the literature. The computerized search identified key words (analgesia, post-operative pain, pain therapy, i.v. patient controlled analgesia, epidural analgesia) in the title, abstract, and Medical Subject Headings (MESH). In addition, a cross-check of the quality of the retrieval method was made by 'hand searching' the full reference lists from review articles and relevant individual papers in four peer reviewed English language anaesthetic journals (*Anaesthesia*, *British Journal of Anaesthesia*, *Acta Anaesthesiologica Scandinavica* and *Anesthesiology*). All publications identified by the search strategy were categorized according to the level of evidence obtained, based on the criteria of the United States Preventive Task Force. Cohort studies, case control studies, and audit reports as well as randomized controlled clinical trials were included in the analysis. Case reports were not included, nor were authors approached for raw or unpublished data. No attempt was made to grade individual papers according to quality. All of the studies used in the analysis were given equal value, as we were interested in predetermined end points rather than the findings of individual studies. One author undertook the data extraction. Figure 1 gives a flow diagram of the review methodology.

Selection criteria

We included articles relating to abdominal, major gynaecological, major orthopaedic, and thoracic surgery. We excluded articles relating to paediatric, day stay and minor surgery, and where the period of observation was less than 24 h. Initial observations made in the recovery room were not included. We did not utilize any study which described a mixed or unusual analgesic technique (e.g. ketamine, clonidine), studies relating to intrathecal opioids, studies of combined spinal/epidural analgesia, nor studies relating to regional analgesic techniques such as interpleural, paravertebral, and lumbar plexus blocks. A full list of all of the studies used in the analysis is included at the end of this paper. Details of all of the excluded studies are available from the authors.

Definitions

We examined measures of safety after major surgery for each of the three analgesic techniques in common practice: patient-controlled analgesia (PCA), epidural analgesia, and i.m. injections as outlined previously. Information was extracted from published studies, which reported variables indicative of respiratory depression and of hypotension. The different measurements have been recorded and where studies involved comparison between drugs (e.g. opioids), the results have been pooled. Where the study compared analgesic techniques, results have been entered separately under each form of analgesia.

Statistical methodology

The mean percentage reporting a given level of pain was found by the method of weighted mean, with weighting by the number of subjects in the group.² When patients were grouped by the method of analgesia, some studies contributed subjects to more than one group. This was ignored in the analysis, possibly resulting in a small loss of power.

Analysis was by estimation of the confidence interval (CI) of the log odds ratio and its CI. The standard error from which the confidence interval was estimated was adjusted for the clustering of the individual clusters within the study and treatment groups, thus allowing for the extra variation, which exists between studies. The log odds was then converted to a percentage by:

$$P=100/[\exp(-\log \text{odds})+1].$$

The effects of analgesic technique and year were tested using logistic regression adjusted for clustering. Analgesic technique was represented by two dummy variables, representing i.v.-PCA and epidural. Both were zero for i.m. analgesia. The significance of the modality effect was tested using the overall χ^2 statistic. To test for analgesic technique adjusted for year, we took the difference between the χ^2 statistics and associated degrees of freedom for the model with modality and year, and for that with year only. All analysis was done using Stata 5.0 (Stata Corporation, College Station, TX).

Results

Respiratory depression

We report on 165 studies relating to respiratory indices. There were a total of 93 027 patients included in papers published between 1956 and 1999, which provided suitable data for analysis. Studies reported ventilatory frequency rate for one, two, or (rarely) all three analgesic techniques. Thus, the total number of study groups may exceed the number of studies in any particular category. A number of other studies were considered appropriate for analysis but were not used because data were not accessible.

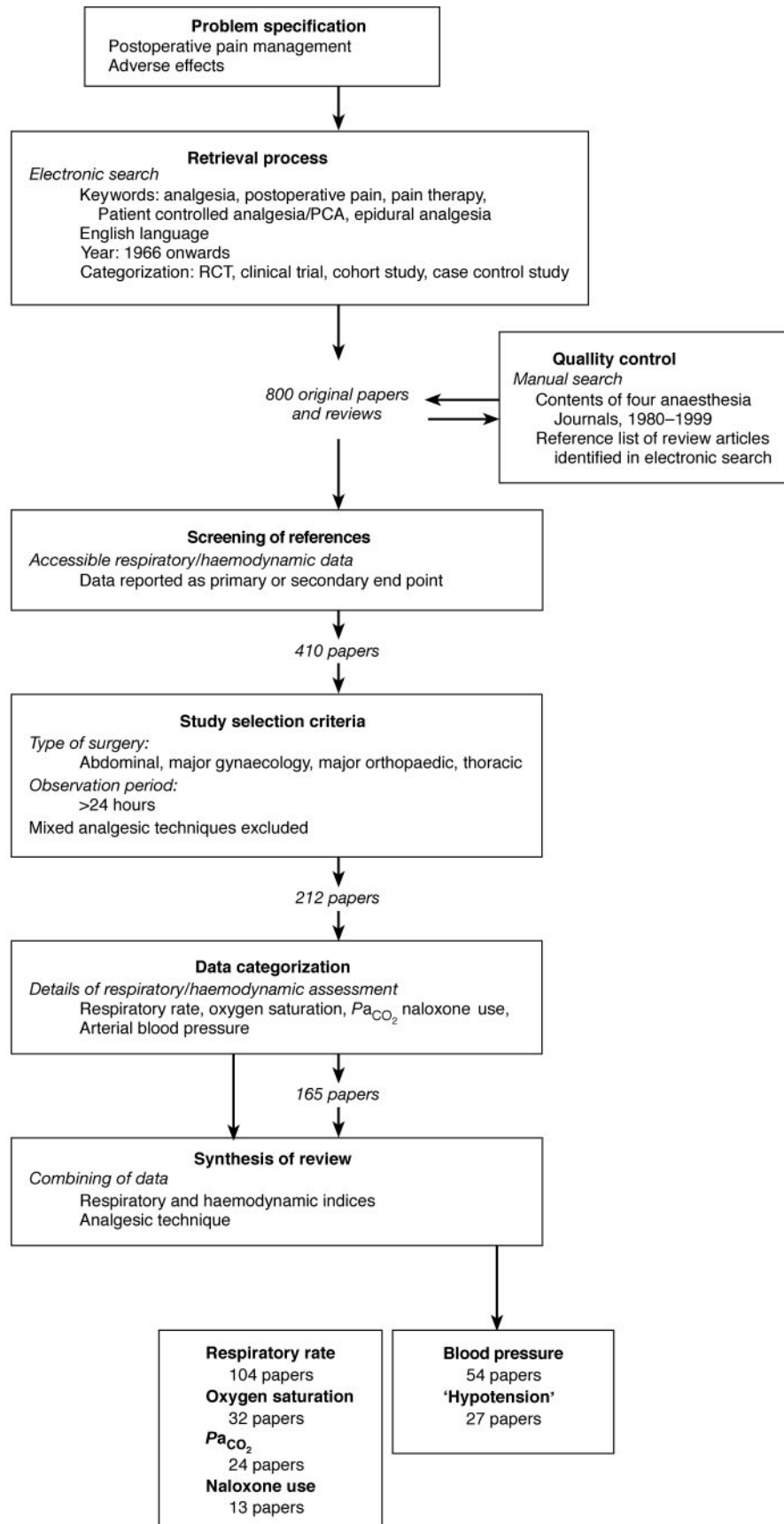


Fig 1 Postoperative pain management: data retrieval flow diagram.

Ventilatory frequency

104 studies reported ventilatory frequency. For studies that reported more than one ventilatory frequency, we used the higher reported ventilatory frequency in our analysis of respiratory depression. We identified 70 study groups that defined respiratory depression as a ventilatory frequency of less than 10 bpm, and 46 study groups that defined it as a ventilatory frequency of less than 8 bpm. This represents a total of 29 607 patients in 116 study groups (1590 patients i.m. analgesia; 6922 patients PCA; and 21 035 patients epidural analgesia). Another 35 studies reported respiratory depression but did not define it; these have not been included in the analysis. The overall mean (95% CI) rate of respiratory depression as defined by a specific ventilatory frequency, whatever the ventilatory frequency the authors of the various studies chose (less than 10 or less than 8 bpm), was 1.1 (0.7–1.7)%. There was no difference in respiratory depression between the three analgesic techniques ($P=0.7$; Table 1).

Oxygen saturation

A total of 24 studies presented data on the number of patients with oxygen saturation below a particular value. As with ventilatory frequency, where more than one oxygen saturation reading was recorded (oxygen saturation less than 90%, less than 85%, or less than 80%), we used the higher reported oxygen saturation in our analysis of respiratory depression. There were 24 study groups that defined respiratory depression as an oxygen saturation of less than 90%, and eight study groups that defined respiratory depression as an oxygen saturation of less than 85% (six studies, which were not included in the analysis, defined it as an oxygen saturation of less than 80%). This represents a total of 1511 patients (246 patients i.m. analgesia; 707 patients PCA; and 563 patients epidural analgesia). The overall mean (95% CI) rate of respiratory depression as indicated by a specific oxygen saturation, as defined by the authors of the various studies, was 17.0 (10.2–26.9)%. The effect of analgesic technique was statistically significant ($P<0.01$) and persisted after controlling for year of publication ($P=0.007$), with i.m. analgesia associated with the highest incidence of oxygen desaturation (Table 2).

Table 1 Reported incidence of respiratory depression as indicated by ventilatory frequency lower than predetermined value

	Number of study groups	Total number of patients	Respiratory depression	
			Mean (%)	95% CI
<i>Analgesic technique</i>				
All	116	29 607	1.1	0.7–1.7%
I.M.	10	1590	0.8	0.2–2.5%
I.V.-PCA	35	6922	1.2	0.7–1.9%
Epidural	71	21 035	1.1	0.6–1.9%

Arterial partial pressure of carbon dioxide

Arterial blood gas analysis was reported in 17 studies. This represents a total of 3166 patients (1508 patients i.m. analgesia; 301 patients PCA; and 1361 patients epidural analgesia). An arterial P_{aCO_2} in excess of 6.5 kPa or in excess of 50 mm Hg was reported as indicating respiratory depression in nine and six studies, respectively. A further two studies did not record the specific level of arterial P_{aCO_2} that had been used. The overall incidence of hypercarbia was 3.3 (0.5–6.0)%. The effect of analgesic technique was significant ($P=0.03$), and persisted after controlling for year of publication ($P<0.0001$); respiratory depression as indicated by hypercarbia was highest with epidural analgesia (Table 3).

Naloxone

The use of naloxone as an indication of an attempt to treat was reported in 10 studies, representing a total of 55 404 patients (71 patients i.m. analgesia; 4691 patients PCA; and 50 642 patients epidural analgesia). However, in both the PCA and epidural groups, there is one overwhelmingly large study, resulting in very narrow CIs. There will be a large non-sampling error, which we cannot estimate and which is not represented in the CI. Overall mean (95% CI) rate of respiratory depression as defined by use of naloxone was 0.3 (–0.1 to 0.6)%. The effect of analgesic technique was highly significant ($P=0.0001$), being lowest with epidural analgesia (Table 4) and persisted after controlling for year of publication ($P<0.0001$).

Table 2 Reported incidence of respiratory depression as indicated by oxygen saturation below predetermined value

	Number of study groups	Total number of patients	Respiratory depression	
			Mean (%)	95% CI
<i>Analgesic technique</i>				
All	32	1516	17.0	10.2–26.9%
I.M.	9	246	37.0	22.6–45.9%
I.V.-PCA	11	707	11.5	5.6–22.0%
Epidural	12	563	15.1	5.6–34.8%

Table 3 Reported incidence of respiratory depression as indicated by P_{aCO_2} above predetermined value

	Number of study groups	Total number of patients	Respiratory depression	
			Mean (%)	95% CI
<i>Analgesic technique</i>				
All	24	3170	3.3	1.4–7.6%
I.M.	6	1508	1.3	0.7–2.3%
I.V.-PCA	4	301	1.3	0.2–7.7%
Epidural	14	1361	6.0	2.1–15.6%

Table 4 Reported incidence of respiratory depression as indicated by naloxone use

	Number of study groups	Total number of patients	Respiratory depression	
			Mean (%)	95% CI
<i>Analgesic technique</i>				
All	13	55 404	0.3	0.1–1.3%
I.M.	3	71	1.4	0.1–12.7%
I.V.-PCA	2	4691	1.9	1.9–2.0%
Epidural	8	50 642	0.1	0.1–0.2%

Change in respiratory depression over time

As part of the analysis, we looked at how the incidence of respiratory depression altered over the time period of the analysis (1980–99). We have reported previously that the analgesic technique varied by year of publication, with i.m. analgesia being the most frequently reported technique in the early part of the period of the analysis, whilst latterly PCA and epidural analgesia have been the most frequently reported techniques.¹ The results of the analysis of ventilatory frequency, P_{aCO_2} and naloxone use indicated that there was a significant decrease in the odds of respiratory depression over time ($P=0.01$, $P=0.0002$, and $P=0.002$, respectively). The relationship between year of publication and respiratory depression persisted after controlling for changes in analgesic technique ($P=0.08$, $P<0.0001$ and $P<0.0001$, respectively), and so was not explained by a change in analgesic technique over time. The results of the analysis of oxygen saturation showed no significant change over time ($P=0.8$).

Cardiovascular depression

We report on 81 studies relating to haemodynamic indices. There were a total of 24 955 patients included in papers published between 1956 and 1999, which provided suitable data for analysis.

Hypotension

Studies varied in their definition of hypotension, commonly tending to present the number of patients with arterial pressure below a threshold level recorded at a particular time. A total of 54 studies presented data on the number of patients with arterial pressure below a pre-defined level, or alternatively data on the number of patients with a decrease of arterial pressure greater than a pre-defined amount. For all of these studies, which reported more than one haemodynamic parameter, we used the first reported arterial pressure in our analysis of hypotension. Thus, there were 27 study groups in which hypotension was defined as a systolic arterial pressure of less than 100 mm Hg and/or a greater than 20% decrease in arterial pressure; 24 study groups in which hypotension was defined as a systolic arterial pressure of less than 90 mm Hg; and a further 23 study groups in which hypotension was defined as a systolic arterial pressure of less than 80 mm Hg and/or a greater than 30% decrease in arterial pressure. Another 27 studies reported haemodynamic depression but

Table 5 Reported incidence of haemodynamic depression (all definitions)

	Number of study groups	Total number of patients	Haemodynamic depression	
			Mean	95% CI
<i>Analgesic technique</i>				
All	111	24 955	4.7	2.8–7.7%
I.M.	12	631	3.6	2.0–6.4%
I.V.-PCA	20	3954	0.7	0.2–2.4%
Epidural	79	20 370	5.5	3.2–9.3%

Table 6 Reported incidence of haemodynamic depression as indicated by all arterial pressure recordings below predetermined level

	Number of study groups	Total number of patients	Haemodynamic depression	
			Mean (%)	95% CI
<i>Analgesic modality</i>				
All	74	20 454	4.9	2.7–8.8%
I.M.	8	506	3.8	1.9–7.5%
I.V.-PCA	11	2473	0.4	0.1–1.9%
Epidural	55	17 475	5.6	3.0–10.2%

did not strictly define hypotension. This represents a total of 22 573 patients (631 patients i.m. analgesia; 3954 patients PCA; and 20 370 patients epidural analgesia). If all definitions of hypotension from the 81 papers are included, the overall rate of hypotension (mean (95% CI)) was 4.7 (2.8–7.7)%. The results were remarkably similar when a definition based on a predetermined level of arterial pressure was used 4.9 (2.7–8.8)%. The effect of analgesic technique was significant, being lowest with PCA and highest with epidural analgesia ($P=0.01$, $P=0.007$; all and strict definitions, respectively). The effect of analgesic technique persisted after controlling for year of publication ($P=0.027$, $P=0.018$; all and strict definitions, respectively). The rates of hypotension are shown in Tables 5 and 6.

Change in hypotension over time

Over the time period of analysis, there has not been a significant decrease in the incidence of hypotension ($P=0.95$ and $P=0.99$; all definitions and strict definition).

Discussion

Respiratory depression is thought to be the most important adverse effect when considering analgesic techniques. A number of criteria have been used to define respiratory depression including ventilatory frequency, percutaneous oxygen saturation, arterial blood gas analysis, and the need to administer respiratory stimulants. Of these, ventilatory frequency is the most frequently used criterion. In a Europe-wide survey of acute pain services, ventilatory frequency was routinely measured in 81% of hospitals, while oxygen saturation was measured in only 41%.³ A ventilatory frequency of less than 10 bpm is the commonest cut off figure,

although a ventilatory frequency of less than 8 bpm is occasionally used. When pulse oximetry is used to identify respiratory depression, an oxygen saturation of less than 90% is most commonly reported, although other endpoints such as saturations of less than 95%, 85% or even 80% have also been used. Occasionally, ventilatory frequency is used in conjunction with pulse oximetry, but not all cases of respiratory depression have both low ventilatory frequency and low oxygen saturation. In a large audit of postoperative analgesia after major surgical procedures, 39 cases of respiratory depression were reported of which only six had a ventilatory frequency of less than 10 bpm, while 23 had an oxygen saturation of less than 90%.⁴ In contrast, arterial blood gas analysis, being relatively invasive, is probably not suitable as a routine practical clinical technique and consequently is much less frequently used. When blood gas analysis is used, a partial pressure of carbon dioxide greater than 6.5 kPa (50 mm Hg) is the most frequently used endpoint. Finally, the need for therapeutic intervention such as the administration of naloxone is a potentially useful criterion, but it is indirect and the decision to use naloxone often will depend on one of the above criteria for respiratory depression being fulfilled.

There is a relative lack of studies assessing the incidence of respiratory depression after intermittent, as required, opioid analgesia. This may be due partly to the fact that oxygen saturation monitoring did not become routine until the mid 1980s, yet most studies of i.m. analgesia were conducted before this date. In one of the few studies that reported oxygen saturations following i.m. opioid analgesia, Jayr and colleagues reported a 13% incidence of desaturation,⁵ which is very similar to the figure of 12.5% reported by Tsui and colleagues,⁶ whilst a 20% incidence of prolonged desaturation was reported in another much smaller study.⁷ Using strict criteria for drug administration, Rawal and colleagues suggested that intermittent opioid analgesia was a safe technique on the basis that no patients required ventilatory support.⁸ These studies, although less comprehensive than comparable studies of epidural or PCA, suggest a somewhat higher incidence of respiratory depression using intermittent i.m. opioid analgesia, an observation borne out by our analysis.

When PCA is used postoperatively, our analysis suggests that low ventilatory frequencies occur in 1.2% of patients, although at least one large study suggests a slightly higher figure.⁹ Arterial desaturation occurred in 11.5% of patients, yet paradoxically, larger studies seem to indicate a lower rate. In one large series of 3016 patients, Schug and Torrie reported an overall respiratory depression rate of 0.56% for i.v. opioids, but many of these were administered by a continuous infusion.¹⁰ Furthermore, respiratory depression in this study was defined by the decision to give naloxone. As has been pointed out previously, there are no clear protocols to dictate when to give naloxone, which at present is by clinician preference. In comparison, our analysis suggests a higher respiratory depression rate of 1.9% based on naloxone administration.

When epidurals are used for postoperative analgesia, the incidence of respiratory depression depends to some extent

on whether or not an opiate has been used in addition to the local anaesthetic. Several large prospective studies indicate that the incidence of respiratory depression varies between 0.2 and 1.2% of patients.^{11–13} This may be lower than the incidence with PCA, although the two have not been formally compared in the same study. One large retrospective survey of epidural analgesia reported an incidence of respiratory depression requiring naloxone administration of 0.4%, but did not define any criteria for the administration of naloxone.¹⁴ In a multi-hospital follow-up survey, Rawal and colleagues found the incidence of delayed respiratory depression to be 0.09%.¹⁵ However, because the survey was conducted over a number of hospitals, it is unclear if they were all using the same criteria to define respiratory depression.

Hypotension has been defined in a number of ways: a decrease in systolic arterial pressure of greater than 20% of a stable preoperative value has been used;¹⁶ as has a greater than 30% decrease,^{17 18} absolute values of systolic arterial pressure of less than 100 mm Hg,¹⁶ or less than 80 mm Hg,^{5 17} and systolic/diastolic arterial pressure of less than 90/60 mm Hg.¹⁸ In a number of studies, hypotension was not defined other than by the need for an intervention. Morphine administration can result in a reduction in arterial pressure, and thus hypotension may be a problem with both PCA and i.m. analgesia as well as with epidural analgesia. However, hypotension may be the result of factors other than the analgesic technique. In a large survey, Tsui and colleagues recorded a 1.9% incidence of hypotension, of which the majority were a result of surgical factors resulting in haemorrhage.⁴ These authors were able to implicate the analgesic technique as the cause of hypotension in only six out of 2509 cases, giving an incidence of 0.2%.⁴ In one of the few reasonably sized reviews of i.m. opioid analgesia that also provided details of arterial pressures, Slack and colleagues recorded a 4% incidence of hypotension.¹⁹ The results of our analysis produced a very similar figure. A slightly higher incidence of 8% has been reported with s.c. morphine.⁵ In contrast, the incidence of hypotension associated with PCA was 0% in two other large studies.^{20 21} There is much more published data on the hypotensive effect of epidural analgesia, with a number of large retrospective surveys suggesting that the incidence of hypotension lies between 2 and 4%.^{18 22–24}

This analysis differs from a formal systematic review with meta-analysis in a number of respects. We did not confine ourselves to randomized controlled trials and no attempt was made to grade individual papers according to quality. All of the studies used in the analysis were given equal value as we were not concerned with the conclusion of the individual study, merely the incidences of respiratory depression and hypotension. We feel that this approach is justified as we were not considering the results of published studies but were concerned with extracting the data from them. It is inevitable in a study of this type that there will be a degree of variability in the analgesic regimens, surgical procedures, and indeed in the data presented. Therefore, a degree of heterogeneity is unavoidable in this analysis. However, we feel that the

large numbers of studies included and the small number of differences sought will reduce the likelihood of statistical heterogeneity. Also, we were mindful of the dangers of over interpretation inherent in searching for causes of heterogeneity. With respect to clinical heterogeneity, we found that the surgical case mix of the studies used was very similar between the three analgesic techniques and we feel confident that the groups mirror 'clinical practice'. Furthermore, at least one subsequent large study has reported incidences of respiratory depression and hypotension with epidural and i.v. opiate analgesia not dissimilar to our own findings.²⁵ The rapid evolution of Acute Pain Services is another source of variability of the data. Many of the studies analysed were reports of the initial experiences of individual centres' Pain Service. It is likely that these services have evolved, and this may well explain the decrease in the odds ratio for respiratory depression over the time period of the analysis. However, this fails to explain why the incidence of hypotension has not changed.

In summary, we present an analysis of published data on the adverse respiratory and haemodynamic effects of acute postoperative pain management. Most Acute Pain Services will use a mixture of techniques, and even when PCA and epidural analgesia are freely available, intermittent administration of opioids will still be used in up to 30% of cases after major surgery.²⁶ Allowing for the variety of definitions, as well as the heterogeneity of the data, the following suggestions for clinical practice can be made. Acute Pain Services should expect respiratory depression related to analgesic technique to occur no more frequently than in 1% of cases as defined by a low ventilatory frequency. If oxygen desaturation is used to indicate respiratory depression, a much higher figure should be expected. I.M. opioid analgesia is associated with a similar incidence of respiratory depression to PCA or epidural analgesia, although naloxone use is greatest in association with PCA. There has been a significant decrease in the incidence of respiratory depression over the course of the last two decades. Acute Pain Services should expect an incidence of hypotension related to analgesic technique of less than 5%. Hypotension occurs most frequently with epidural analgesia and least often in association with PCA. These figures may be helpful to Acute Pain Services in setting standards of care.

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Appendix 1

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Appendix 4

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