THE EFFECT OF ROUTINE VS. P.R.N. POST-OPERATIVE ANALGESIA ON PULMONARY COMPLICATIONS: A MULTICENTER TRIAL

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Significant pulmonary complications have been estimated to occur in 20 percent to 70 percent of patients following abdominal surgery (Lattimer, Dickman, Day, Gunn Schmidt, 1971). Atelectasis is the most frequent pulmonary complication occurring during the first 48 hours (Bartlett, Brennan, Gazzaniga & Hanson, 1973; Rigg, 1981; Wightman, 1968). The belief that the pathogenesis of atelectasis and pneumonia are the same (Coryllos and Birnbaum, 1929) and that unresolved atelectasis leads to lung infection (Guis, 1966; Henderson, 1929) suggests that any degree of atelectasis renders the patient at risk to develop further pulmonary pathology and an extended hospital stay. Herein lies the importance of the prevention of atelectasis in post-operative patients.

A number of demographic, disease, life-style and treatment variables have been shown to influence the rate of development of atelectasis (Rigg, 1981). Any influence that improves underventilation in dependent lung regions is shown to increase this tendency. Hence, when the discomfort of an abdominal or thoracic incision inhibits inspiration, the abdominal pain induces voluntary and reflex muscle spasm, affecting primarily the abdominal muscles and the diaphragm. This leads to more rapid but shallow respirations, poorly expanding the lower lobes of the lungs (Pflug & Bonica, 1977). Secretions accumulate and when the entering gas does not exceed the closing volume of the alveoli, the alveoli begin to collapse. Paradoxically, excessive analgesic control of abdominal pain may also lead to hypoventilation and predispose the patient to pulmonary complications (Rigg, Vedig & Isley, 1981). A variety of medication regimes and routes of administration of medication have been studied in the attempt to resolve this dilemma (Egbert

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The Canadian Journal of Nursing Research *Winter 1991, 23(4), 7-22*

& Bendixen, 1964; Jayr, et al., 1988; Nayman, 1979; Rutter, Murphy & Dudley, 1980; Rybro, 1982).

The most common form of pain control is p.r.n. intramuscular injections, whereby patients receive medication at their request, within the limits of the existing protocol, commonly every three to four hours as necessary. It is possible, however, that by the time a patient is in enough pain to ask for medication, the adaptive response to pain, such as muscle splinting and anxiety which create low lung volumes and impaired clearance of mucous, has already begun. These sequelae could be averted by preventing the pain from reaching that intensity through the use of a regular schedule of pain medication in the first 48 hours following surgery (Austen, Stupelton & Mather, 1980; Graves et al., 1983). The efficacy of pain control rather than pain relief requires further investigation.

This interpretation is consistent with the results of studies found in the literature (Egbert & Bendixen, 1984; Nayman, 1979), which noted fewer pulmonary complications in patients with adequate pain control from continuous intravenous infusion of morphine. It is possible that a reduction in post-operative pulmonary complications could be obtained with a regular, timed intramuscular medication regime. In so far as intramuscular injection, rather than intravenous infusion, is the conventional route for the administration of pain medication after surgery, this is an important issue from the perspective of treatment.

The primary purpose of this study was to test the hypothesis that regularly timed pain medication, rather than p.r.n. schedules, would reduce the incidence of post-operative complications when intramuscular injection was the route of choice. There is some evidence in the literature that obesity (Naimark & Cherniak, 1960; Rawal et al., 1984; Thoren, 1954) and the habit of smoking (Finley & Ladman, 1972; Morton, 1944; Pearce & Jones, 1984; Wightman, 1968) predispose patients to developing pulmonary complications following surgery; as such, control of these variables, as well as the effect of attention, was required.

In summary, the existing literature, while limited by small samples or weak designs, nevertheless suggests that inadequate ventilation may be an important causal factor in the development of atelectasis. Patients who are obese or who smoke may be at greater risk. Decreased ventilation in post-operative patients may be attributable to a number of inhibiting effects. While abdominal pain and its treatment have been implicated as mediating factors in the development of pulmonary complication (Pflug, 1974; Spence & Smith, 1971) some more recent studies have been unable to demonstrate the superiority of any analgesic method in this regard (Jayr, et al. 1988; Raval, et al. 1984). Consequently, the essential argument involves two opposing per-

spectives relative to post-operative pain control in the prevention of pulmonary complications. These perspectives, are either that 1) scheduled analgesics are better than p.r.n. because of improved pain control and hence reduced complications; or 2) that p.r.n. analgesics are superior because scheduled analgesics improve pain control at the cost of increased complications. This study will attempt to address this controversy.

Methods

Three hundred and forty elective abdominal surgical patients, 16 to 70 years of age, from the practices of six surgeons at three general hospitals, were initially identified as candidates for study. Thirty-one of these patients were excluded because of physical impairment that could affect pulmonary outcomes or because of language difficulty; six were missed and twenty-five refused to give consent for chest x-ray. The remaining 278 consenting and eligible patients were stratified according to surgeon, smoking habit and obesity. Patients in each strata were randomly allocated to one of three study groups and, for the first 48 hours post-operation, were to receive either analgesia every three hours; or p.r.n. analgesia; or p.r.n. analgesia plus vital signs monitoring every three hours. The third group was an attention placebo group to control for the regular attention that accompanied regularly scheduled analgesia administration. The study group allocation was done using a blocked randomization procedure established by a person external to the investigating group.

The type of intramuscular analgesia used in all three study groups was predominantly Demerol, although occasionally Morphine 10 mg. was used. The dosage of Demerol varied between 50-100 mg. in all three study groups, largely as a function of the size and age of the patient. Thus, the principle difference in study groups was one of a regular versus p.r.n. schedule of administering the analgesia.

After subjects were allocated to study groups, thirty subjects received co-interventions that could affect outcome or did not have a post-operative chest x-ray. A further sixty-eight subjects were not maintained on the appropriate study regimen. Because of these events, the following three separate studies emerged.

The "management trial" (N=278) assessed the effects of regular or p.r.n. pain medication regimes on subjects allocated to the three study groups. In the real clinical world, these subjects might also have received other interventions which could have affected outcome. The "effectiveness trial" (N=248) assessed the effects of regular or p.r.n. pain medication regimes on subjects who did not receive additional interventions that could have affected outcome. The "efficacy trial" (N=180) assessed the effects of regular or

p.r.n. pain medication regimes and also attention on subjects who were maintained on the appropriate regimen.

The comparability of the three study groups was reassessed following the exclusion of the thirty patients who had received co-intervention, and again following the exclusion of the sixty-eight patients who had not been maintained on the appropriate study regimen. In the "effectiveness trial" (N=248), the three analgesia study groups were comparable in all sociodemographic, biological and clinical variables, except for the frequency of heavy smokers and nasogastric tubes. The group with regular analgesia orders had more heavy smokers than the group with p.r.n. analgesia orders (2-tailed Fisher's exact p=.02), and more than the group with p.r.n. analgesia/regular vital signs (2-tailed Fisher's exact p=.06). The group with p.r.n. analgesia/regular vital signs monitoring regimen had the smallest proportion of subjects with nasogastric tubes with the major difference between this group and the p.r.n. group (1-tailed Fisher's exact p=.05).

When the three study groups were assessed following the exclusion of subjects who were not adequately maintained on the appropriate regimen ("efficacy trial"), they were found to be comparable from a statistical perspective. However, the proportion of heavy smokers was greater in the regular analgesia group (10.6%), compared with 2.8% in the p.r.n. analgesia group and 4.6% in the p.r.n. analgesia/regular vital signs "attention" group. Further, the proportion of subjects under the age of 60 years was greatest in the p.r.n./regular vital signs group (27.9%), followed by the regular analgesia groups (16.7%) and the p.r.n. analgesia group (14.4%). Also, secondary surgical procedures were reported for a greater proportion of the p.r.n./regular vital signs groups (34.9%) than for the regular analgesia group (33.7%) or the p.r.n. group (18.3%). These differences between study groups may be relevant in terms of post-operative pulmonary outcomes or length of stay.

The principle outcome measure or "gold standard" for pulmonary pathology was evidence of lung pathology on a chest x-ray taken on the fourth day after surgery, with the day of surgery counted as day one. For study purposes, one research radiologist interpreted all available chest x-rays and was masked to the previous clinical and radiological interpretations, the nature of the study and had no access to the patient's clinical data. Inter- and intra-rater agreement substudies were done and Fleiss generalized kappa's ranged between .61 and .83, respectively. A further measure of pulmonary status was created by having the research radiologist make a judgement on the severity of lung pathology from pre- to post-operative x-ray. A clinically important progression in lung pathology was defined as an advance of two or more categories on a five-category scale of severity. The highest temperature recorded each day, for the first four days after surgery, was obtained as a

secondary measure of pulmonary pathology. However, temperature was found to be of little diagnostic value when the sensitivity, specificity, positive and negative predictive values of this test were calculated (Roberts, Barnes, Pennock & Browne, 1988).

Results

As indicated in Figure 1, there were no statistically significant or clinically important differences in the presence of lung pathology on the fourth day after surgery among subjects receiving three regimes of analgesia within the Management Trial (X^2_2=2.43,NS); or the Effectiveness Trial (X^2_2=3.12,NS); or the Efficacy Trial (X^2_2=3.12,NS).

In addition, across the three trials, there were no statistically significant differences in a clinically important progression of lung pathology by the fourth day of surgery among the analgesia treatment groups (Management: X^2_2=3.66,NS; Effectiveness: X^2_2=3.42,NS; Efficacy: X^2_2=3.267,NS). The results are illustrated in Figure 2.

The direction of the differences between the analgesia groups, however, remained the same across all three trials. Surprisingly, the lowest rate of post-operative lung pathology and clinically meaningful progression in lung pathology was found in the p.r.n./regular vital signs group followed by the regular analgesia group and then by the p.r.n. analgesia group which had the highest rate of lung pathology.

There was a statistically significant difference among the three randomized analgesia groups in the mean number of doses of analgesia given over the first 48 hours (ANOVA $F_{2.245}$=47.9, $p<.001$). The regular analgesia group received more doses than either of the other two groups (Scheffe $p<.05$). The expected difference between the p.r.n. analgesia group and the p.r.n./regular vital signs group was not found. The results are shown in Table 1.

In an attempt to determine the factors that were associated with a pre- to post-operative clinically important increase in lung pathology a discriminant function analysis was conducted on those subjects with a lung change score. Standardized canonical discriminant function co-efficients for the variables, listed in order of their ability to distinguish between subjects with and without a clinically meaningful progression in lung pathology after surgery, included age (.7359) and gender (.5996). Older males were the two factors that correctly classified 65.18% of the 163 subjects who had been maintained on the appropriate study regimen. Increased age was the main factor.

FIGURE 1

The Effect of Analgesia Regimes on Lung Pathology in the Management, Effectiveness and Efficacy Trials

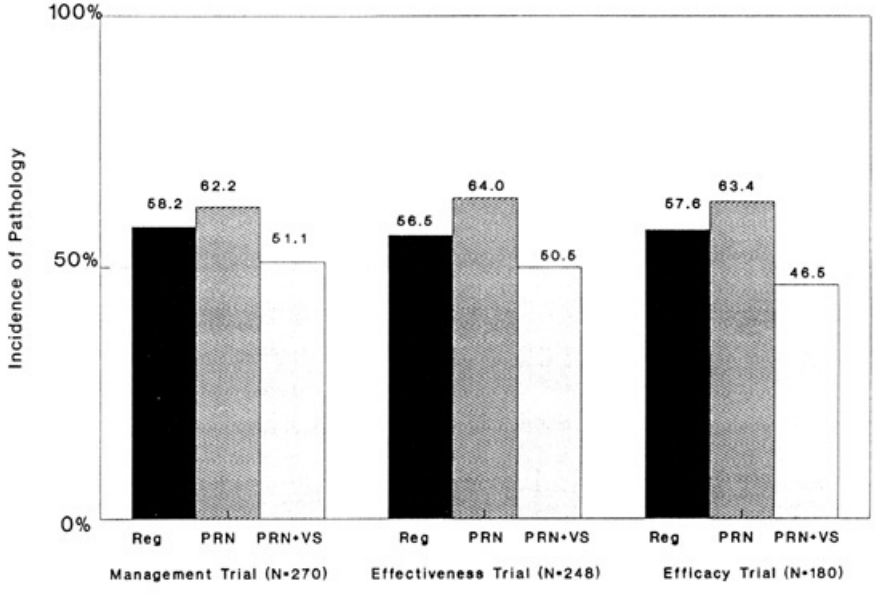

FIGURE 2

The Effect of Analgesia Regimes on the Incidence of a Clinically Important Progression of Lung Pathology in the Management, Effectiveness, and Efficacy Trials

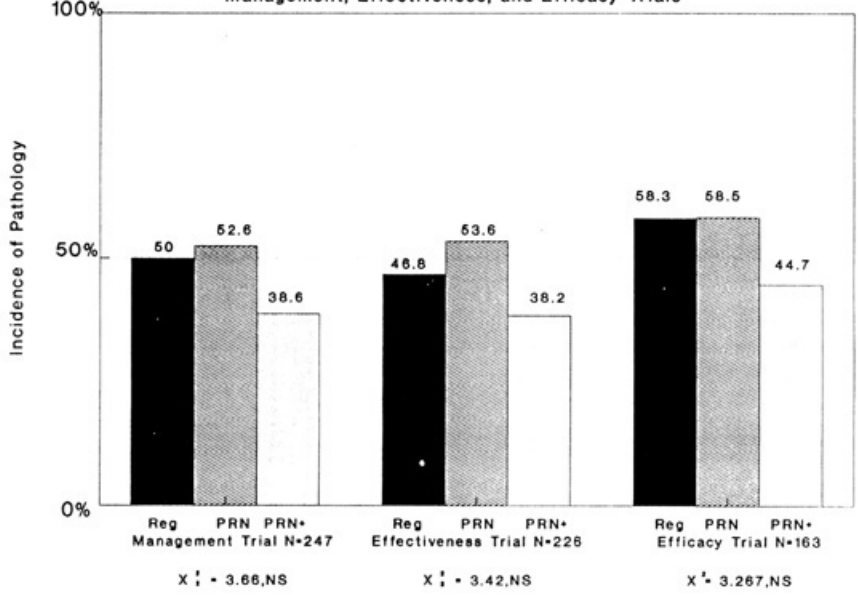

Table 1

Comparison of Mean Number of Analgesic Doses Administered in First 48 Post Operative Hours Under Three Schedules of Prescription

	Regular Analgesia Group	PRN Analgesia Group	PRN/Regular Vs Analgesia Group
Number of Doses of Demerol equivalents	x (SD)	x (SD)	x (SD)
	13.86 (3.2)	9.93 (2.8)	9.77 (3.12)

*** ANOVA, $F_{2,245} = 47.9, p < 001$**

The relative risk of developing a clinically important progression of lung pathology following surgery was assessed with the 163 subjects who had been maintained on the appropriate analgesia regimen. The Woolfe Relative Risk Analysis was conducted, with the subjects separated into five age groups. Comparisons were done with pairs of analgesia study groups, (i.e., regular versus p.r.n.; p.r.n. vs vital signs; regular vs vital signs). The results are shown in Tables 2, 3 and 4. The overall risk of developing a clinically important progression of lung pathology was essentially the same for those patients who received p.r.n. medications as compared to those who received the regular pain medication regimen (1:14). The main differences were noticed among 30-49-year-old subjects where the risk of developing lung pathology was 1.61 to 1.75 times greater if these subjects were in the p.r.n. group versus the regularly scheduled group (Table 2).

When subjects receiving p.r.n. medication were compared to those receiving regular vital signs and p.r.n. medication, the overall risk of developing a meaningful progression in lung pathology was *twice as great in the p.r.n. medication group* as in the regular vital signs/p.r.n. medication group. The main differences were in subjects over 50 years of age, particularly those subjects aged 50 to 59 years where the risk was 4.5 times greater if the subject was a member of the p.r.n. medication group versus the vital signs/p.r.n. group (Table 3).

The risk of developing a clinically important progression in lung pathology post-surgery was 6.67 times greater again for those subjects aged 50-59 years who received pain medication on a regular 3-to 4-hour regimen, versus p.r.n. medication with regular vital signs monitoring. For subjects aged 30-49 years, the risk was slightly less for the regular pain medication group but, overall, the risk was twice as great in that group versus the regular vital signs group (Table 4).

In summary, the risk of developing a clinically important progression in lung pathology after surgery was lowest overall for subjects who had received scheduled vital signs monitoring along with a p.r.n. medication regimen, as compared to either the scheduled analgesia or p.r.n. analgesia regimen. This difference in risk was pronounced in subjects over 50 years of age and in those less than 30 years of age when they received a regularly scheduled analgesic rather than scheduled vital signs with p.r.n. medications. There was some benefit in receiving regular pain medication if subjects were between 30 and 50 years of age.

Table 2

The Relative Risk By Age Group of Developing a Clinically Important Progression of Lung Pathology From Pre Operation To Post Operation (Day 4) with P.R.N. Medication or With Regular Pain Medication

	Analgesia Study Regimen				
	PRN Medication		Regular Medication		Relative Risk
Age Group	Clinically Important Increase in Pathology				
	Yes N	No N	Yes N	No N	
16-29 years	1	8	2	9	.56
30-39 years	10	8	7	9	1.61
40-40 years	7	8	4	8	1.75
50-59 years	9	4	10	3	.68
60-70 years	7	3	6	2	.78
Total	34	31	29	31	1.17

Woolfe Analysis adjusted relative risk = 1.14

Table 3

The Relative Risk By Age Group of Developing a Clinically Important Progression in Lung Pathology From Pre Operation to Post Operation (Day 4) With P.R.N. Medication or With Regular Vital Signs Plus P.R.N. Medication

	Analgesia Study Regimen				
	PRN Medication		Regular Vital Signs		Relative Risk
Age Group	Clinically Important Increase in Pathology				
	Yes N	No N	Yes N	No N	
16-29 years	1	8	1	9	1.13
30-39 years	10	8	2	2	1.25
40-40 years	7	8	2	3	1.31
50-59 years	9	4	3	6	4.50
60-70 years	7	3	5	5	2.30
Total	34	31	13	25	2.11

Woolfe Analysis Adjusted Relative Risk = 2.04

Table 4

The Relative Risk by Age Group of Developing A Clinically Important Progression In Lung Pathology From Pre Operation to Post Operation (Day 4) With Regular Pain Medication or With Regular Vital Signs plus P.R.N. Medication

	Analgesia Study Regimen				
	PRN Medication		Regular Medication		Relative Risk
Age Group	Clinically Important Increase in Pathology				
	Yes N	No N	Yes N	No N	
16-29 years	2	9	1	9	2.00
30-39 years	7	9	2	2	.78
40-40 years	4	8	2	3	.75
50-59 years	10	3	3	6	6.67
60-70 years	6	2	5	18	3.00
Total	29	31	13	25	1.80

Woolfe Analysis Adjusted Relative Risk = 2.05

Discussion

The main purpose of this study was to determine the efficacy of regularly scheduled analgesia versus p.r.n. regimen in reducing the incidence or severity of pulmonary atelectasis, or both. Across the three trials (management, effectiveness and efficacy) regularly scheduled analgesia as a post operative regime was not superior to a p.r.n. regime in preventing atelectasis or in delaying the progression of pulmonary pathology following surgery. Surprisingly, the study group that received p.r.n. medication with a regularly scheduled vital signs regimen (attention placebo) had the lowest clinical rate of post operative pulmonary complications, while the p.r.n. group without the regular attention had the highest rate. Interestingly, these groups did not differ in the mean number of analgesic doses administered within the first 48 hours post operatively.

The relative high-risk analysis indicated that the analgesia regime most beneficial in reducing the risk of post operative lung pathology depended on the age group of the subjects. Regular medication was a benefit only in the 30 to 49 year group. P.R.N. medication plus regular vital signs was the most beneficial regimen overall and in particular with the over 50 year old subjects.

The variables that were found to discriminate between subjects with clinically important progression in lung pathology were age and gender. Male subjects who were older were more likely to have an important progression in pathology. Further, males who smoked were more likely to develop atelectasis and have a clinically important progression of lung pathology after surgery than females who smoked.

The direction of these results suggest that there are multiple variables that interact in order to produce post operative pulmonary complications. When risk reduction analyses were used instead of statistical analyses, the minimal movement group that accompanied the regular attention of vital signs along with p.r.n. pain medication, resulted in 35% risk reduction in the development of a clinically important progression of lung pathology, compared to the risk among patients receiving p.r.n. medication alone. On the other hand, regular pain medication reduced the risk by 8% when compared to the p.r.n. medication group which was in the predicted direction but not statistically significant.

The effect of gender on the study results is obvious for a number of variables. It was an important prognostic factor in post operative atelectasis and increased the incidence of atelectasis among smokers. In addition, being male was a predictor of analgesic doses given in the first 48 hours within the regular medication group (Weir et al., 1990).

These unpredicted findings suggest that analgesic dosing (p.r.n.) and clinical treatment (such as the presence of nasogastric tubes and taking vital signs on a regular schedule) interacted with position and movement (especially freedom to move) to reduce pulmonary complications in younger (under 60 years) non-heavy-smoking, males. Because there are no data on the patients' response to the administered analgesic, it is not possible to identify the role that pain control had in this multidimensional equation. It is apparent that post operative pain management must consider more variables than the schedule of analgesic administration in light of the potential to reduce the risk of pulmonary complications.

Future studies of post operative pulmonary complications should test the effect of levels of pain control coupled with levels of ventilatory change (through types of pulmonary management) among men and women of different ages. In addition, in future studies, the necessity for stratifying subjects according to age, prior to study group allocation, should be apparent, given the influence that age has in affecting pulmonary outcomes post operatively.

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Supported by Ontario Ministry of Health, Health Research Grant 00644.

RÉSUMÉ

Étude multicentre de l'effet sur les complications pulmonaires de l'administration post-opératoire systématique c. prn d'analgésiques

L'efficacité comparative d'un mode de prescription d'analgésiques régulier c. prn dans la prévention de l'atélectasie post- opératoire a été évaluée sur 278 sujets, dans le cadre d'une étude randomisée tenant compte de l'effet du tabagisme, de l'obésité, de l'attention régulièrement prodiguée et de la comparabilité des groupes d'étude par rapport aux variables parasites.

Les patients à qui on faisait subir des changements de position minimes et qui recevaient donc un "placebo d'attention" et des analgésiques prn avaient 35 % de chances en moins de complications pulmonaires cliniquement importantes. De plus, les patients recevant des analgésiques à intervalles réguliers avaient 8 % de chances en moins d'être atteints de ces mêmes complications que les patients recevant des analgésiques prn. Les répercussions de ces résultats sur la conception et la conduite d'études ultérieures sont analysées.