Original Article

How Effective Are Supplementary Doses of Opioids for Dyspnea in Terminally Ill Cancer Patients? A Randomized Continuous Sequential Clinical Trial

Pierre Allard, MD, PhD, FRCPC, Claude Lamontagne, MD, CCFP, FCFP, Pascale Bernard, MSc, and Chantale Tremblay, MD

Maison Michel Sarrazin (P.A., C.L.), Departments of Social and Preventive Medicine (P.A., P.B.), and Family Medicine (C.L.), Laval University, Quebec City, Canada; Department of Medicine (C.T.), Centre Hospitalier Universitaire de Montréal, Pavillon Notre-Dame, Montreal, Province of Quebec, Canada

Abstract

Supplementary doses of opioids are recommended to relieve dyspnea in terminally ill cancer patients. We conducted a randomized continuous sequential clinical trial to evaluate their efficacy. We recruited 33 terminally ill cancer patients from three palliative care centers, all of whom had persistent dyspnea after rest and treatment with oxygen. Patients formed 15 successive pairs matched on route of administration. Within each pair, the order of allocation was randomly assigned, one patient receiving 25%, the other 50% of his 4-hourly opioid dose. Five measurements of dyspnea intensity and respiratory frequency were made during 4 hours of follow-up. For each pair, a preference was attributed to the more effective regimen. The two regimens received an almost equal number of paired preferences (8 vs. 7). Overall, both mean dyspnea intensity and respiratory frequency decreased significantly relative to baseline. Dyspnea reduction was relatively greater in patients with initially low and moderate dyspnea intensity. In terminally ill cancer patients with persistent dyspnea, 25% of the equivalent 4-hourly dose of opioid may be sufficient to reduce both dyspnea intensity and tachypnea for 4 hours. J Pain Symptom Manage 1999;17:256–265. *© U.S. Cancer Pain Relief Committee, 1999.*

Key Words

Dyspnea, terminal cancer, randomized clinical trial, opioids

Introduction

Dyspnea, the distressing awareness of breathing, is a problem encountered frequently as death approaches in terminally ill cancer patients. In the National Hospice study, dyspnea prevalence increased as the patient approached death, and was 49%, 54%, and 57% at 6, 3, and 1 week, respectively.[1] In such patients, the aim of treatment is to ameliorate the perception of breathlessness rather than its cause.[2]

Supplemental oxygen has been shown to reduce dyspnea intensity in hypoxemic cancer patients.[3] Morphine is recognized as the main-

Address reprint requests to: Pierre Allard, MD, PhD, CHA, Pavillon du Saint-Sacrement, 1050 Chemin Sainte-Foy, Quebec City, Province of Quebec, Canada, G1S 4L8.

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stay of dyspnea treatment,[4,5] but only two studies have been conducted in dyspneic cancer patients who were already receiving morphine for pain control. In 15 dyspneic cancer patients, the subcutaneous administration of morphine at 2.5 times their usual dose provided a significant improvement in dyspnea intensity for about 2 hours without any significant change in respiratory rate.[6] In a placebo-controlled crossover study of 10 dyspneic cancer patients on regular morphine, the intensity of dyspnea was significantly improved after a test dose of morphine which was 50% higher than the regular dose.[7]

An increase in the total daily opioid dose by as much as 50% has been recommended for patients who suffer from dyspnea which is unrelieved by rest and oxygen.[8] However, palliative care clinicians often follow a more cautious strategy. Instead of immediately increasing the usual dose of opioid prescribed for pain relief, they make available on demand supplementary doses consisting of at least a quarter of the current 4-hourly dose.[9] Although this approach would seem attractive, its efficacy needs assessment.

Thus, we conducted a randomized continuous sequential controlled trial to compare the efficacy of two supplementary dosing regimens of opioids on dyspnea in terminally ill cancer patients who were already receiving opioids regularly for pain relief. The regimens studied consisted, respectively, of one-quarter and one-half of the current 4-hourly opioid dose.

Methods

Procedures

From November 1994 to June 1997, study patients were recruited from three palliative care centers located in the Province of Quebec, Canada. The coordinating nurse, assisted by at least one of the investigators, provided detailed information sessions to all physicians and nurses involved in patient's care in the three participating centers. In each center, a research nurse was trained in study procedures, and a detailed study manual was available at all times in each ward. Candidate patients were those who met the following criteria: (a) they had persistent dyspnea at rest; (b) they were already regularly receiving opioids for pain relief, either orally or subcutaneously; (c) they were alert and not confused; and (d) according to the treating physician, there was no contraindication to study participation. Patients were not considered as candidates if: (a) they were in acute respiratory distress for which an immediate intervention was mandatory; (b) they had received three or more rescue doses for breakthrough pain during the previous 24 hours; and (c) they were receiving only so-called "weak" opioids (codeine and codeine derivatives) or fentanyl for pain relief.

After being fully informed of the study aim and procedures, candidate patients who provided written consent entered a 90-minute baseline observation period to verify their eligibility. During this period, supplemental oxygen was provided and bed rest was strongly recommended. Every 30 minutes, a research nurse took measurements of dyspnea intensity and respiratory frequency. At the end of the observation period, eligibility was confirmed only if patients met the following criteria: (a) they had been able to rate the intensity of their dyspnea on a 10 cm visual analogue scale; (b) dyspnea intensity at 90 minutes measured at least 2.0; (c) there was no cognitive impairment according to a simplified Folstein Mini-Mental State Examination.

Immediately after confirmation of eligibility, the pharmacist prepared a supplementary dose consisting of one-quarter or one-half of the equivalent 4-hourly current opioid dose, according to a random allocation schedule. The rescue dose was sent to the ward for immediate administration by the bedside nurse. The route of administration for a given patient was the same as the scheduled opioid regimen.

Double-blinding was ensured as follows. Using a special form, the attending physician prescribed both supplementary opioid doses (25% and 50%), using the equivalent 4-hourly dose as the reference dose. From the randomization list, the pharmacist determined the appropriate supplementary dose to be administered. An oral dose was prepared with the liquid formulation of the current opioid and mixed with water up to a volume of 10 ml in a disposable syringe container. A subcutaneous dose was delivered in a disposable syringe covered with an opaque tape. Thus, neither the patient nor the research nurse knew whether the supplementary dose administered consisted of a quarter or half of the regular 4-hourly dose.

During a 4-hour follow-up period, the research nurse took five consecutive measurements of dyspnea intensity and respiratory frequency, at 30, 60, 120, 180, and 240 minutes, respectively. For ethical reasons, no restriction on cointerventions was imposed during this follow-up. Regularly scheduled or "as-needed" (p.r.n.) medications for breakthrough pain or dyspnea were recorded.

The primary outcome variable was dyspnea intensity as perceived by the patient. Dyspnea intensity measurements were carefully standardized using a 10 cm standard visual analog scale with a horizontal moving ruler. The scale was anchored on two arrows, one at the left extremity by the word "None," and the other on the right extremity by the word "Intolerable." Numerical values on the back of the scale were not shown to the patient. In obtaining dyspnea intensity ratings from the patient on the visual analogue scale, the research nurse used the following procedure. For the first intensity rating, the research nurse moved the ruler to the right up to the point indicated by the patient. For all subsequent ratings, the nurse asked the patient whether his difficulty in breathing was the same, better or worse than at the previous rating. If dyspnea intensity was the same, the nurse recorded the previous rating. If dyspnea intensity was considered by the patient as better or worse than previously, the nurse moved the ruler in the appropriate direction up to the point indicated by the patient. Previous ratings of dyspnea intensity were made available to patients because research on visual analogue scales has shown that individuals overestimated present sensation in serial measurements of subjective states when previous scores are not seen.[10,11]

At completion of data collection for each patient, data on dyspnea intensity and respiratory frequency were transmitted by facsimile to the coordinating center. Data were transmitted without delay to the biostatistician (P.B.) to allow for a rapid completion of the sequential analysis diagram.

Continuous Sequential Design and Statistical Analysis

To allow for a constant monitoring of potential efficacy differences between the two supplementary doses, this study was designed as a continuous sequential trial for "paired preferences."[12] This study design is appropriate to assess the relative merits of two active treatments by comparing a series of qualitative preferences in favor of one or other treatment. Ethical imperatives precluded the inclusion of a placebo group in the present study. Despite 90 minutes of rest and oxygen, study patients had persistent dyspnea at intensity that warranted immediate administration of a breakthrough opioid dose, which is considered as an essential component of dyspnea treatment in very sick cancer patients already receiving opioids for pain control.

Under this sequential design, patients entered the trial in pairs, one on each supplementary dose regimen, the order of treatment allocation being at random. As the pharmacokinetics of oral and subcutaneous opioids differ substantially, pairs were matched on route of administration. Thus, oral and subcutaneous pairs were considered separately.

When the second patient of each pair completed follow-up, an ad hoc analysis was conducted to determine which patient would receive the "paired preference." The preference was allocated to the patient who experienced the greater reduction in mean dyspnea intensity relative to the prerandomization level. The paired preference was then plotted as a 1 cm diagonal line on a preset diagram, which was filled out as successive pairs of patients were evaluated. The diagram had upper, lower, and middle boundary significance limits. Reaching the upper and lower limits would indicate a superior efficacy for the 25% and 50% supplementary dose regimen respectively, whereas reaching the middle limit would indicate no difference in efficacy. The diagram was constructed so that there would be a 95% probability of detecting a treatment difference if one supplementary dose regimen was truly better in 85% of pairs. The minimum number of paired preferences required for attaining any one of the boundary significance limits was 16 (32 paired patients). None of the investigators had access to the sequential diagram throughout the study. However, all collaborators knew that they would be informed immediately if a boundary significance limit was attained.

The comparability of the two randomized groups with respect to patient characteristics and cointerventions was evaluated with simple

descriptive statistics and appropriate tests for differences. Simple figures were used to illustrate the change in mean dyspnea ratings and respiratory frequency over time according to each supplementary dose group. To assess whether the supplementary dose was effective to reduce dyspnea intensity and respiratory frequency, we used the following strategy of analysis. For each patient, we computed the difference between the mean prerandomization and postrandomization values, and we summed these paired differences for each outcome separately. Then, we tested the null hypothesis that the overall mean in the paired differences (for dyspnea intensity and respiratory frequency separately) was equal to zero in the overall sample of 33 patients, using the paired *t*-test with 32 degrees of freedom. Finally, in an exploratory analysis, we examined the supplementary dose effect according to the severity of dyspnea at baseline.

Results

Patients

Eligibility was confirmed in 33 of the 35 patients who were considered candidates (Fig. 1). Two patients were not randomized because their dyspnea was almost entirely relieved (intensity rate <2.0) by the initial 90-minute period of rest and supplemental administration of oxygen. Of the 33 study patients, 61% were recruited in the main coordinating center, and 21% and 18% in each of the two other centers respectively. Of the 20 patients on oral opioids, 11 and nine patients randomly received one-quarter and one-half of their equivalent 4-hourly opioid dose, respectively. Of the 13 patients on subcutaneous opioids, seven and six patients received one-quarter and one-half of their supplementary doses, respectively. Thus, nine oral pairs and six subcutaneous pairs were available for the paired preference analysis.

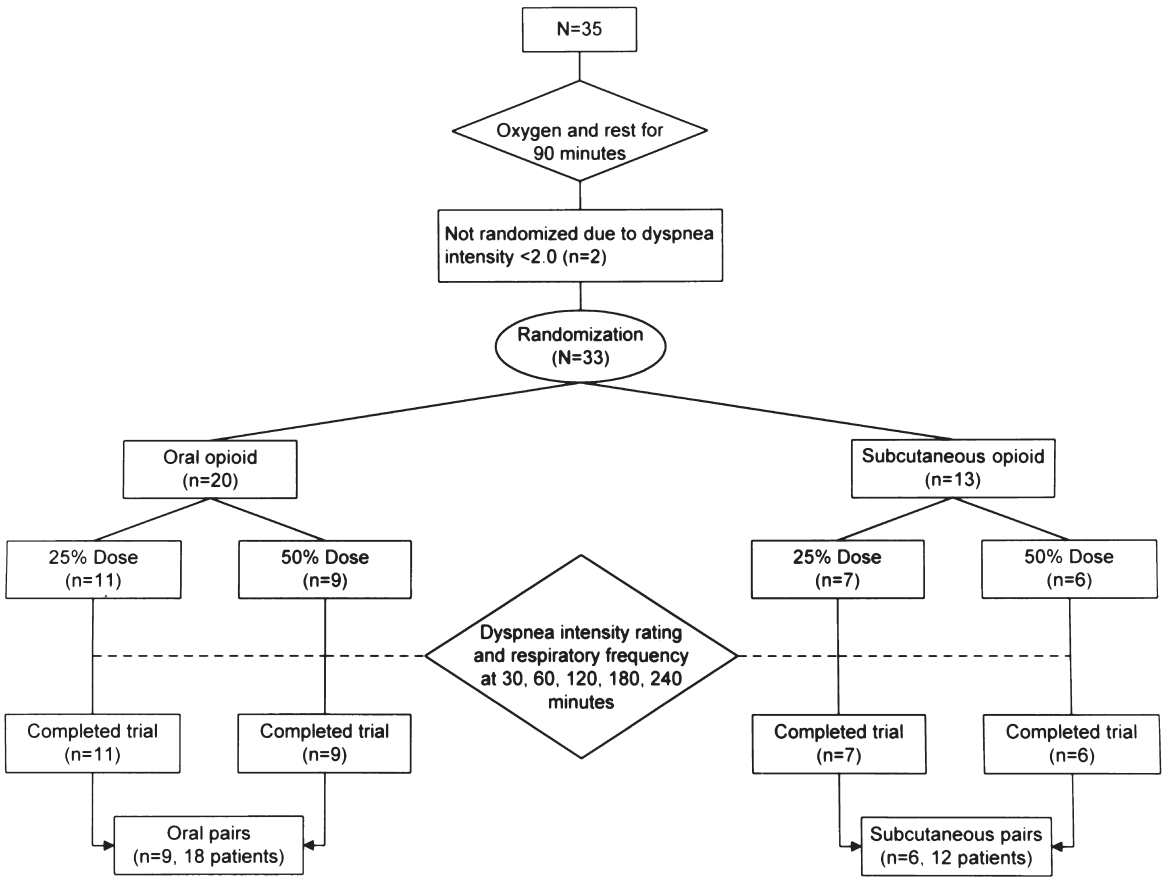

Fig. 1. Profile of the continuous sequential clinical trial.

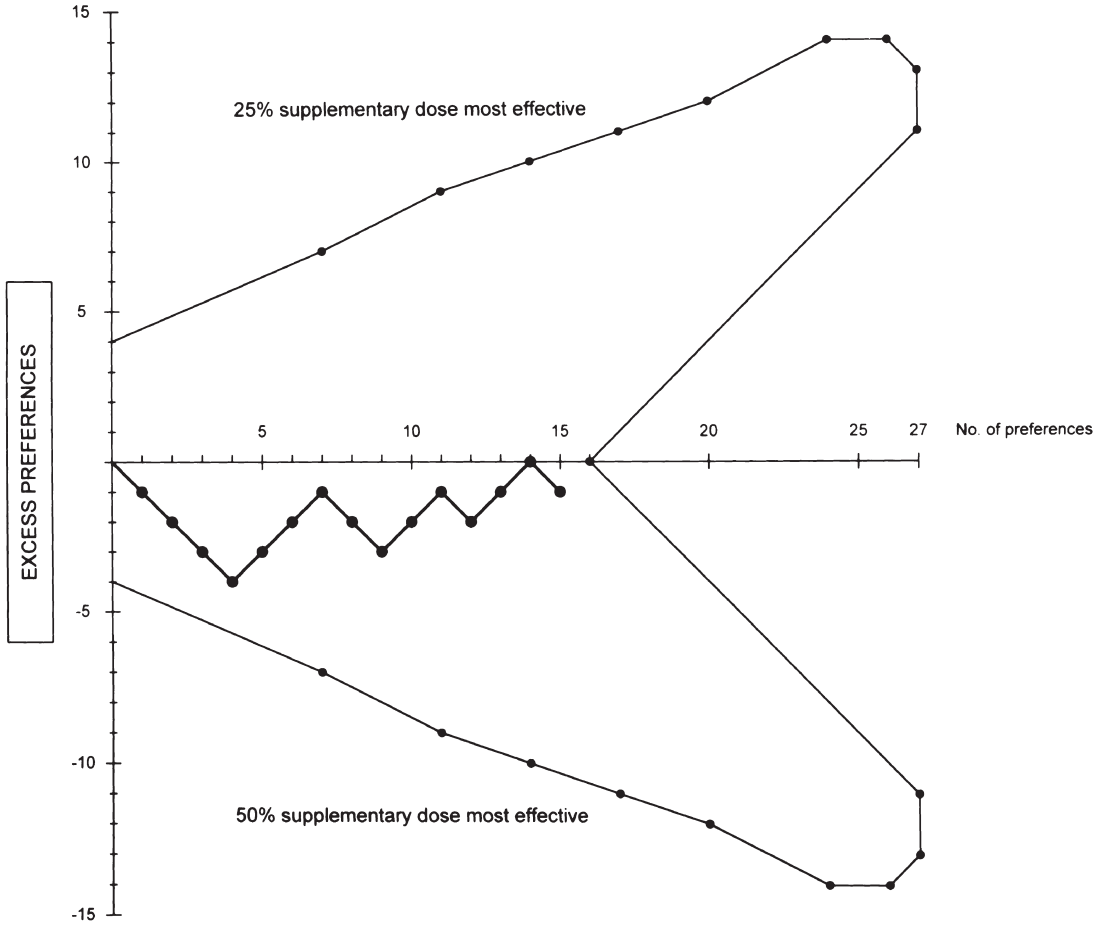

Fig. 2. Sequential analysis diagram of paired preferences in favor of the 25% or 50% supplementary dose of opioids.

Paired Preference Analysis

As shown in Fig. 2, although the first four paired preferences were in favor of the 50% supplementary dose, this early trend was not sustained. Overall, the 25% and 50% supplementary doses received an almost equal number of paired preferences (8 vs. 7). The upper and lower boundary significance limits indicating a superior treatment effect in favor of either supplementary dose regimen were not attained. As three of the 33 study patients remained unpaired, at least one paired preference was missing to attain the middle boundary for concluding formally that no significant difference was present between the two supplementary doses.

Treatment Effect on Dyspnea and Tachypnea

The two treatment groups were similar with respect to age, sex, and primary cancer sites (Table 1). In addition, the two groups were comparable with respect to the mean dyspnea intensity and respiratory frequency at baseline. The frequency of cointerventions during follow-up was similarly low in the two groups. Patient survival among those who received one-quarter of the regular dose of opioids was slightly less than among those in the other group (median days of survival: 14.5 vs. 19).

As presented in Fig. 3, mean postrandomization dyspnea intensities were slightly lower than baseline prerandomization values, and the treatment effect was almost identical in patients who received one-quarter or one-half their regular opioid dose. Overall, the mean difference between pre- and postrandomization dyspnea intensities was 0.86 (SD = 1.10, paired *t*-test: $P < 0.0001$). A reduction in mean respiratory frequencies also occurred after the administration of the 25% and 50% supplementary dose (Fig. 4). The overall mean difference between pre- and postrandomization respiratory frequencies was 1.56 (SD = 2.28,

Table 1
Patient Characteristics by Group of Randomization

Patient characteristics	Overall ($n = 33$)	Opioid dose as percent of the 4-hourly regular dose: 25% ($n = 18$)	Opioid dose as percent of the 4-hourly regular dose: 50% ($n = 15$)	Significance of between-group difference (P value)
Age				
Mean	63.3	61.3	65.7	0.23
Median	66	65	67	—
Sex				
Females	57.6%	55.6%	60.0%	0.80
Primary cancer site				
Lung/Pleura	21	12	9	0.92
Breast	6	3	3	
Other	6	3	3	
Baseline measurements				
Mean dyspnea intensity	4.5	4.6	4.4	0.71
Mean respiratory frequency (breaths/min)	20.3	20.1	20.6	0.82
Cointerventions				
Breakthrough dose for pain or dyspnea	7	3	4	0.67[a]
Nebulized medications	16	8	8	0.61[a]
Median days before death	15	14.5	19	

[a]Fisher exact test.

paired t-test: $P = 0.0004$). The decrease in respiratory frequency was sustained up to 240 minutes after the supplementary dose administration.

As shown in Table 2, there was only a slight and inconsistent increase in baseline respiratory frequency by severity of dyspnea. Thus, tachypnea was not a good indicator of the severity of dyspnea experienced by the patient. The beneficial effect of the supplementary dose on dyspnea was inversely related to baseline dyspnea intensity (Table 2), the reduction in mean dyspnea intensity being approximately three times greater in patients with initially low dyspnea intensity than in those with high dyspnea intensity (33.1% vs. 11.1%, Kruskall-Wallis rank test: $P = 0.1017$). In contrast, the beneficial effect on tachypnea was inconsistently related to baseline dyspnea intensity.

Discussion

Internal Validity

Several characteristics of this sequential trial strengthen its internal validity. Despite the small number of study patients, randomization was effective in achieving balance in baseline patient characteristics between the two groups. Moreover, the two groups remained comparable after complete follow-up in terms of cointerventions. Double-blinding was used to prevent bias in the reporting and assessment of dyspnea intensity and respiratory frequency, the two response variables. The method of measurement of dyspnea intensity was carefully standardized to avoid overestimation of subjective ratings by the patient. All randomized patients completed the trial. Thus, potential bias related to patient withdrawal or loss to follow-up were avoided. Finally, as oral and subcutaneous pairs were considered separately, confounding by factors dependent on the route of administration was prevented.

This study was one short of the minimum number of pairs required in the sequential plan (three patients remained unpaired). An additional paired preference in favor of the 25% supplementary dose would have led to a more definitive conclusion of equal preferences between the two regimens. An additional paired preference in favor of the 50% supplementary dose would have left the diagram still open. Despite this inherent inferential limitation, the overall analysis presented in Figs. 2–3 strongly suggests that the two supplementary dose regimens provided a similar beneficial effect on both dyspnea and tachypnea. The probability that the sequential analysis diagram of Fig. 1 led to a false-negative conclusion stating that the number of preferences in favor of one or the other supplementary dose of opioid is equal is relatively small. If, in fact, 10 or 11 of

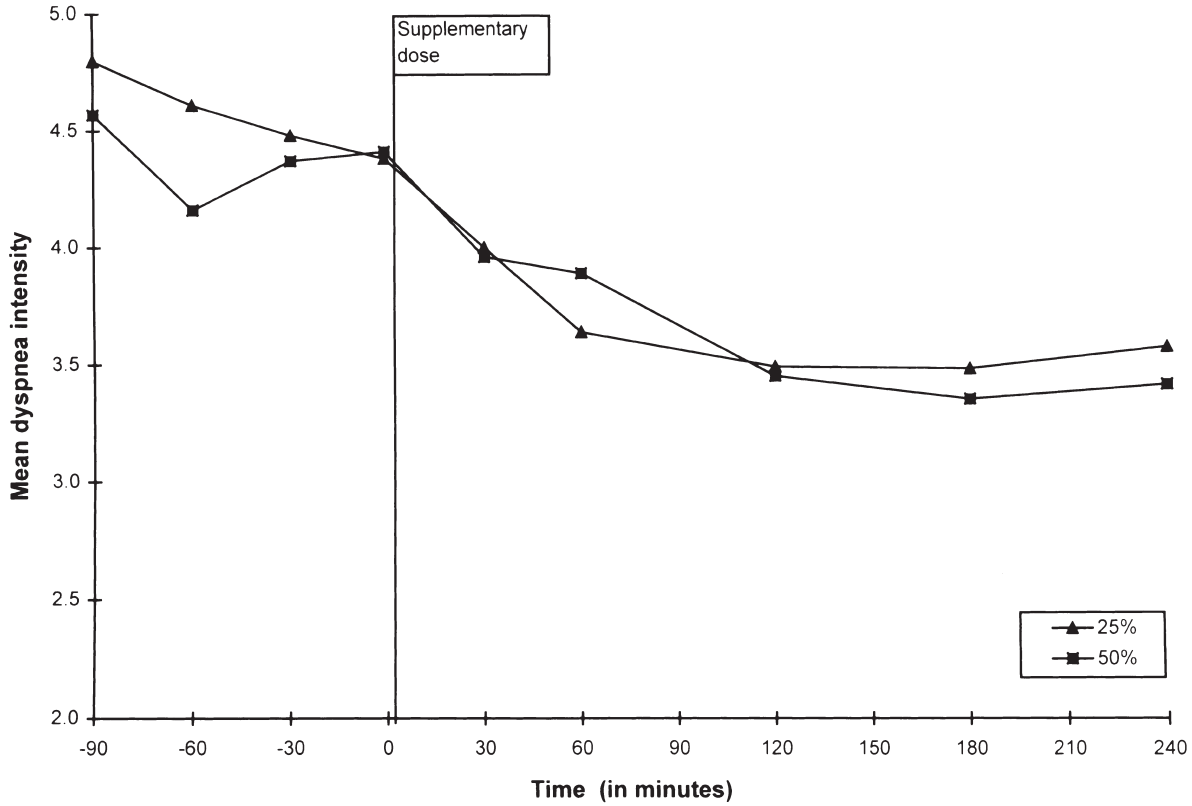

Fig. 3. Mean dyspnea intensity before and after randomization.

the 15 preferences were in favor of any one of the two supplementary doses, the probability of reaching the upper or lower boundary limits of significance would have been about 35% and 59%, respectively.

External Validity

Study patients were recruited in three Canadian palliative care units, each with 10 to 15 beds. We believe that entry criteria were such that study patients were representative of those that most clinicians would, a priori, consider as candidates for the administration of supplementary opioid doses for the relief of dyspnea. These patients should remain dyspneic despite rest and oxygen, and they should not suffer from acute respiratory distress that requires emergency intervention.

In this study, the follow-up period was restricted to 4 hours. This restriction was chosen at the design stage because the clinical condition of dyspneic patients admitted for terminal care is very unstable. Thus, we believed that a longer period of follow-up would have made impossible the conduct of a randomized controlled trial on this important clinical problem. A limitation is that the results of this study are not relevant for cancer patients who are not receiving regular opioids for pain control.

Comparison with Other Studies

The findings of this trial complement the results of two studies that examined the efficacy of a single subcutaneous injection of morphine in dyspneic advanced cancer patients unrelieved by bed rest and oxygen. In one uncontrolled study, 15 cancer patients receiving oral morphine for pain relief were administered, at the time of their scheduled analgesic dose, a single subcutaneous dose of morphine equivalent to 2.5 times their regular dose.[6] A significant decrease in dyspnea intensity was observed without change in respiratory rate. Dyspnea intensity was at its lowest 45 minutes postinjection (from 6.8 to 3.4), remained stable for about 30 minutes, and returned progressively

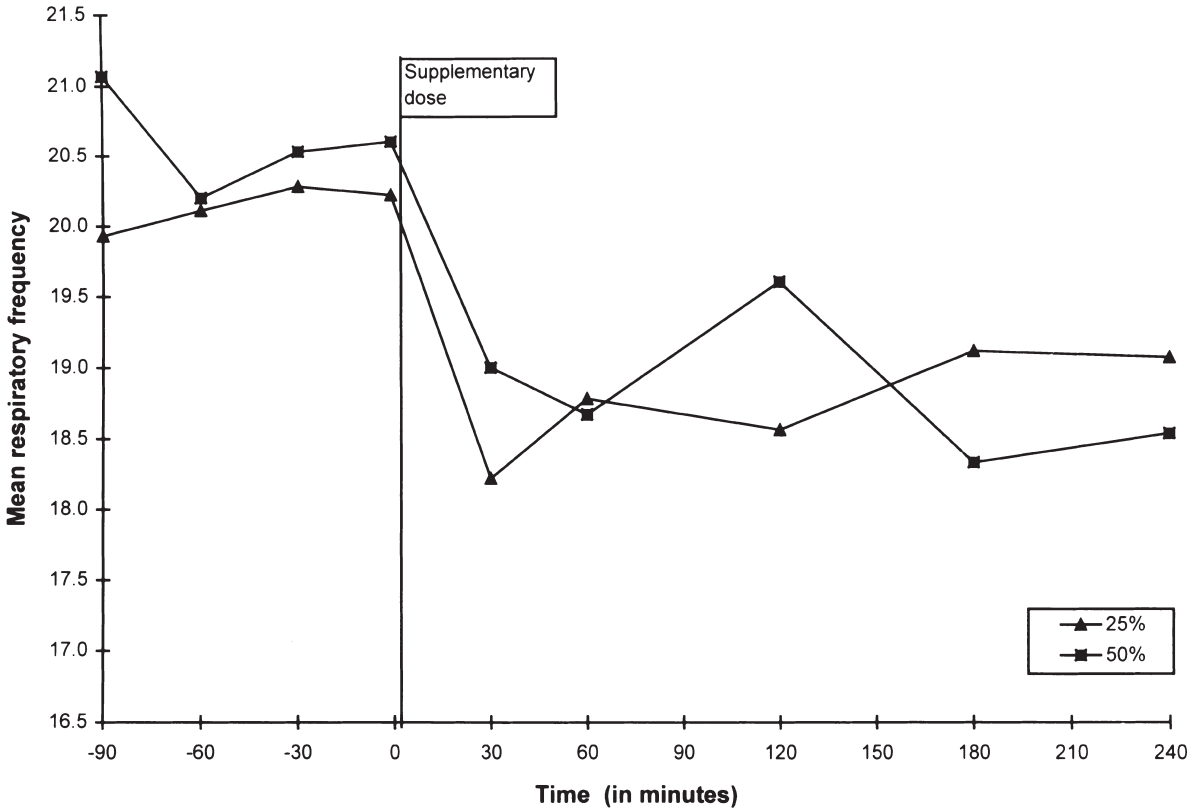

Fig. 4. Mean respiratory frequency before and after randomization.

toward baseline levels after 150 minutes. In a placebo-controlled trial, 10 consecutive patients with terminal cancer on intermittent subcutaneous morphine for pain were administered a single subcutaneous injection of morphine at a dose 50% higher than the regularly schedule dose (which is equivalent to a 50% supplementary dose administered at the time of the regular morphine dose).[7] The maximal reduction in intensity of dyspnea (from 3.0 at baseline to 1.4) was recorded at 60 minutes but the respiratory frequency of 22 per minute at baseline remained unchanged. The results of our study provide evidence that supplementary doses of opioids consisting of only one-quarter of the regular 4-hourly dose may be effective to reduce dyspnea intensity for as long as 4 hours. Moreover, it shows that a slight reduction in tachypnea may also be obtained. Our study is also the first to report that the beneficial effect of morphine is greater in patients with low and moderate dyspnea intensity than in those with high intensity.

In this trial, the relief in dyspnea intensity was accompanied by a concomitant decrease in respiratory frequency. This observation does not imply a causal relationship between dyspnea relief and tachypnea reduction. In the two uncontrolled studies mentioned above on morphine efficacy, dyspnea relief was observed but without any concomitant change in respiratory frequency.[6,7] Dyspnea relief induced by morphine is a complex phenomenon still poorly understood, involving diminished ventilatory response to hypoxia and hypercapnia,[13] and bradycardia and hypotension secondary to peripheral vasodilatation.[14]

Clinical Implications

This study has important clinical implications. First, in dyspneic terminally ill cancer patients who are unrelieved by rest and oxygen, supplementary doses of opioids representing only one-quarter of their regular dose may efficiently reduce both dyspnea intensity and tachypnea, and the beneficial effect may extend for

Table 2
Effect of the Supplemental Opioid Dose According to Mean Baseline Dyspnea Intensity

Mean baseline dyspnea intensity	No. of patients	Mean baseline respiratory frequency	Percent decrease in Dyspnea[a] intensity (95% CI)	Percent decrease in Respiratory[b] frequency (95% CI)
Low (1.83–3.00)	9	19.3	33.1 (1.0–65.4)	10.5 (2.0–18.9)
Intermediate (3.01–5.00)	12	21.6	22.7 (12.9–32.6)	4.1 (0.0–8.2)
High (5.01–7.35)	12	19.9	11.1 (3.0–19.2)	7.4 (3.3–11.4)

[a]Kruskall-Wallis rank test: $P = 0.1017$.
[b]Kruskall-Wallis rank test: $P = 0.2823$.

as long as 4 hours. Second, there is no obvious advantage of using more than one-quarter of the regular dose. However, as only a slight benefit is expected in patients with initially high dyspnea intensity (greater than 5/10), very careful monitoring of treatment effect is imperative. These patients may need significant sedation to obtain a sufficient relief, and their risk of acute respiratory distress is certainly very high.

Our study leaves important questions unanswered. For how long should a dyspneic patient be managed with only supplementary doses of opioids? Should the regular opioid dose be maintained at the baseline level as long as the dyspnea intensity remains controlled, or should we increase the regular dose by one step as soon as possible? These questions are almost impossible to address in a single rigorous controlled trial such as the one reported here. Thus, more studies on dyspnea in terminal cancer patients are clearly needed.

Such studies are difficult to conduct. The clinical condition of dyspneic patients with advanced cancer is very unstable and usually deteriorating fast. As illustrated in the present study, randomized trials based on sequential design for paired preferences offer interesting advantages for palliative care research when the study outcome is immediate symptom relief. Patients are entered into the study serially in time, and analysis of preferences is made continuously on a preset diagram. As the design implies a continuous monitoring of treatment effect, the trial may be brought to a close early in the presence of any significant treatment effect.

Conducting research on dyspnea is also difficult because of the essential requirement of obtaining informed consent. Most cancer patients are simply too sick to be asked for an informed consent as they become dyspneic. For this reason, the recruitment period of the present study had to be extended over two and a half years. One possibility to overcome this limitation might be to obtain informed consent well in advance in patients at risk of developing dyspnea. However, this procedure was not used because the ethics committee judged that it may cause unnecessary anxiety in frail patients receiving palliative care.

In conclusion, our study demonstrated, in terminally ill cancer patients with dyspnea unrelieved by rest and oxygen that (a) a supplemental opioid dose consisting of one-quarter of the regular dose is sufficient to decrease dyspnea intensity and tachypnea during the subsequent 4-hour period, and (b) the supplemental dose is more effective in patients with initial dyspnea intensities of less than 5/10. Although these findings may enlighten the decision-making process in managing dyspnea, the palliative care clinician must rely on clinical skills and ongoing assessment to find the optimal management strategy for each cancer patient suffering from dyspnea.

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Dr. William Fraser who revised the manuscript. In the middle of this study, we were deeply sorrowed by the sudden death of our colleague, Dr. Claude Synnott, who was supervising the study in one of the participating centers.

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