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ORIGINAL ARTICLE

Non-invasive Ventilation in Cancer Patients: a historically matched controlled study

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ABSTRACT

BACKGROUND: Prognosis of cancer patients requiring Invasive Mechanical Ventilation (IMV) is poor. Various studies conducted mainly in patients with haematological malignancies have shown that Non-Invasive Ventilation (NIV) is associated with improved results

OBJECTIVE: To compare NIV with IMV in patients with various malignancies. An assessment was also made of the possible bias in our results due to recent improvements in IMV.

MATERIAL AND METHODS: A historically matched controlled study of NIV versus IMV. Forty seven patients treated by NIV were matched with 47 historical controls treated by IMV. Matching was performed according to 5 variables: type of cancer, leucopenia, allogeneic bone marrow transplantation, SAPS II score and reason for ventilation.

RESULTS: Duration of ventilation and of hospitalisation were significantly (p=0.001) shorter in the NIV group; 48% of patients treated with NIV were discharged from the hospital versus 23% of those treated by IMV (p=0.08). NIV was statistically more effective than IMV in solid tumours, non transplanted and non leucopenic patients. Contrary to the period before 1996, when the analysis was restricted to the IMV matched cases, in the period since 1996, no difference in terms of mortality between IMV and NIV was found.

CONCLUSIONS: In comparison with IMV, NIV in cancer patients: is associated with two significant advantages: reduction in ventilation duration and reduction in hospitalisation stay.

ABBREVIATIONS:
ICU = intensive care unit
NA = non applicable

KEY WORDS: *non-invasive ventilation, cancer, intensive care, mechanical ventilation*

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INTRODUCTION

During the last decade, Non-Invasive Ventilation (NIV) has been increasingly used for the management of respiratory failure in the ICU. It is currently considered as the preferred initial treatment for acute exacerbation of chronic obstructive pulmonary disease [1], for acute haemodynamic oedema [2] and for acute hypoxaemic respiratory failure occurring in immunocompromised patients [3,4]. In cancer patients, NIV has been shown in two case-control studies [5,6] to be associated with improved results

when compared to Invasive Mechanical Ventilation (IMV). In both, the majority of the patients had haematological malignancies and the study design was retrospective, using historical controls. Nonetheless, Azoulay et al [5] have also observed improved results in IMV patients treated in the more recent period (after 1996) when compared to patients treated before 1996.

In a preliminary study [7], we reported our own experience, showing that in a random cancer patients population, NIV was an effective form of ventilatory support, with a 58% and 43% discharge rate from the ICU and the hospital, respectively. These results appeared very encouraging, and they compared favourably to those reported in oncological patients treated with IMV [8], including our own, where, in a series of 168 cancer patients, we were able to extubate 26%, and discharge 22% from the ICU and 17% from the hospital [9]. Yet such good results render ethically unjustifiable the performance of a randomised trial to demonstrate the superiority of starting intensive care management with NIV versus IMV in cancer patients. These considerations led us to perform a historically matched controlled study in order: 1) to determine if NIV, as opposed to IMV, results in a better outcome for cancer patients with solid tumours and haematological malignancies, and 2) to assess if the improved results with NIV reported in the literature were not explained by a less effective intensive care management in the early IMV period (before 1996).

MATERIAL AND METHODS

Potential candidates for the present study were patients requiring mechanical ventilation in the medical ICU of our cancer hospital, between November 1985 and April 2004. To be eligible, cancer patients had to have respiratory failure, defined as: severe dyspnoea at rest; profound hypoxaemia in room air or during nasal oxygen therapy and/or severe hypercapnia; acute pulmonary haemodynamic oedema non-responding rapidly to diuretics and oxygen; clinical decision that the patient required support with mechanical ventilation. Patients without underlying neoplastic disease and/or admitted for elective surgery were ineligible. Patients with "DNR" ("do not resuscitate") orders were excluded because, by definition in our hospital, they are not eligible for IMV. Patients who were intubated for cardio-respiratory arrest, for haemodynamic instability, and/or with a Glasgow scale score for coma <8 were ineligible because they were considered as absolute indications for IMV. Patients with excessive secretions, agitation, inadequate cooperation or severely impaired mental status were also excluded from the NIV group. In case of multiple admissions for a given patient, only the first episode of ventilation was taken into account. No ethics approval was required for this historically matched controlled study.

Every NIV patient was matched with a corresponding IMV patient for 5 variables: type of cancer (solid tumour versus haematological tumour); allogeneic bone marrow or stem cell transplantation (yes versus no); leucopenia (white blood cell count $<1000/mm^3$ versus $\geq 1000/mm^3$) at ICU admission; equivalent gravity score (SAPS II) at admission (equivalence defined as an absolute difference ≤ 5); reason for ventilation (hypoxaemic respiratory failure versus hypercapnic respiratory failure versus acute pulmonary haemodynamic oedema).

The following information was retrospectively retrieved from the medical chart of each patient: demographic data at ICU admission (age, gender); characteristics of the disease: type of cancer, time since diagnosis, prior treatment, including bone marrow or stem cell transplantation, cancer phase [10] (diagnostic, curative, controllable but no more curable, pivotal or palliative care; patients at palliative stage should not be admitted for critical care under our ICU policy), leukocyte count at ICU admission (leucopenia was defined as a leukocyte count <1000 cells/mm^3); reason for ICU admission and reason for mechanical ventilation; SAPS II scores calculated on the basis of the most disturbed value recorded during the first 24 hours of stay after ICU admission; period of ICU admission; duration of ventilation and of ICU hospitalisation; ICU and hospital discharge.

IMV was performed with the Servo ventilator (Siemens, Solna, Sweden) or with the Evita 4 ventilator (Dräger, Lübeck, Germany). NIV, available since January 2000 in our institution, was provided with a standard facial mask by the BiPAP Vision ventilator (Respironics Inc, Murrysville, USA). Positive end expiratory pressure (between 3 and 11 cm H_2O), pressure support (between 7 and 24 cm H_2O) and FiO_2 were adjusted to patient's tolerance and to arterial blood gases. NIV was used for a minimum of 1 hour every 4 hours but sometimes continuously, if necessary, to maintain blood arterial haemoglobin oxygen saturation > 90%. When the patient's condition improved, we progressively weaned NIV by 2 cm H_2O decrements over a few hours. Patients who failed NIV underwent tracheal intubation and were mechanically ventilated. Criteria for endotracheal intubation included persistence of respiratory failure or haemodynamic instability, but also the need to protect the airways to manage copious tracheal secretions or alveolar bleeding and intolerance to mask ventilation.

On the basis of our previous studies [7,9], we have calculated that we needed to have 51 patients by arm to show that NIV allows improvement of success rate (discharge from ICU) to 50% from an expected IMV success rate of 20% with a statistical power of 90% and an α error risk of 5% (two-tailed comparison). Our study was stopped after the recruitment of 47 patients in each arm. Indeed as NIV seemed effective, we used it more and more as first choice for ventilation. Therefore, the problem was that, to obtain further patients to match, we needed to consider patients treated as controls over too long a period. It should be noted that during this

period, 17 patients with DNR order were treated by NIV, but were excluded from the present study according to our above mentioned criteria.

MacNemar tests were used to compare matched observations for binary outcomes. Paired Wilcoxon tests were used to compare continuous variables. Fisher test was used to compare categorical variables. To adjust the comparison of the two intervention strategies for covariates that had a significant impact on the probability of death, we used logistic regression models with estimation of odd ratios and calculation of 95% confidence intervals. A p value < 0.05 was considered as statistically significant.

RESULTS

Patients' characteristics including demography, neoplastic disease and respiratory failure requiring ventilatory support are described in table 1. A patient in the NIV group, presented with renal adenocarcinoma who benefited from an allogeneic bone marrow transplantation, was considered as equivalent to transplanted haematological patients in terms of immunosuppression and matched with a haematological patient. Two haematological patients had autologous marrow transplantation; in each group they were matched with non-transplanted haematological patients. Twenty-four patients in the NIV group were included in our previous report [7], which was only a feasibility study about the place of NIV in cancer patients (enrolment until November 2001). Ventilatory support was provided during the first 24h ICU admission in 33 patients in the NIV cohort and 22 in the IMV one. About 40% of the matched patients had haematological malignancies and 60% solid tumours.

Results obtained by both techniques are shown in table 2. Duration of ventilation support was shorter (p=0.001) with NIV than with IMV. ICU hospitalisation stay was significantly (p=0.01) reduced in the NIV group. Twenty-six patients (55.3%) in the NIV group and 13 patients (27.6%) in the IMV group were discharged alive from the ICU (p=0.01). Twenty-three patients (48.9%) in the NIV group and 11 (23.4%) patients in the IMV group were discharged alive from the hospital (p=0.08).

Subgroup analyses are shown in table 3 for ICU discharge and in table 4 for hospital discharge. NIV was particularly effective in the non-leucopenic, non-allo-transplanted and solid tumours subgroups as well as in the subgroup of patients matched with controls treated before 1996. Median duration of ventilation support for the subgroup matched with controls treated before 1996, was 2.5 days (range: 1- 26) with NIV and 10.5 days (0 – 47) with IMV (p=0.004), respectively and for the subgroup matched with controls treated since 1996, 3 days (range: 1 – 24) with NIV and 10 days (0 – 36) with IMV (p=0.008), respectively. Median duration of ICU stay for the subgroup matched with controls treated before 1996, was 10 days (range: 1- 42) with NIV and 15.5 days (1 – 47) with IMV (p=0.28), respectively and for the subgroup matched with controls treated since 1996, 8 days (range: 1 – 26) with NIV and 19 days (1 – 172) with IMV (p=0.02), respectively.

Among the patients in the NIV group, 15 (31.9%) required endotracheal intubation after failure of NIV and only one of them was discharged alive from ICU and hospital. Reasons for intubation were persistence of respiratory failure (n=6), septic shock (n=4), abundant alveolar haemorrhage (n=3) and alteration of consciousness (n=2).

TABLE 1. Patients characteristics.

Arm	NIV	IMV
Gender		
- male	28 (59.6%)	31 (66.0%)
- female	19 (40.4%)	16 (34.0%)
Age (years) - median (range)	56 (23-78)	56 (23-79)
Type of tumour		
1) Solid tumours	29 (61.7%)	28 (59.6%)
- Lung cancer	13 (27.6%)	12 (25.5%)
- Other	16 (34 %)	16 (34 %)
2) Haematologic malignancies	18 (38.3%)	19 (40.4%)
- Acute leukaemia	10 (21.3%)	13 (27.6%)
- Other	8 (17 %)	6 (12.7 %)
Cancer phase		
- diagnostic	2 (4.3%)	4 (8.5%)
- curative	22 (46.8%)	20 (42.6%)
- control	22 (46.8%)	17 (36.2%)
- pivotal	1 (2.1%)	6 (12.8%)
Cancer duration (months) - median (range)	11 (0-156)	12 (0-180)
Allogeneic bone marrow or stem cell transplantation	9 (19.1%)	9 (19.1%)
Leucopenia (<1000/mm^3)	10 (21.3%)	10 (21.3%)
Leukocyte level (mm^3) - median (range)	5790 (10-42370)	8400 (0-79500)
SAPS II - median (range)	34 (16-64)	34 (16-66)
Cause requiring mechanical ventilation		
- Hypoxemic respiratory failure	34 (72.3%)	34 (72.3%)
- Hypercapnic respiratory failure	10 (21.3%)	10 (21.3%)
- Acute haemodynamic oedema	3 (6.4%)	3 (6.4%)
Median PaO_2 (range) in mm Hg	55 (33-93)	67 (43-200)
Median $PaCO_2$ (range) in mm Hg	37 (18-88)	43 (28-69)
Median pH (range)	7.39 (7.18-7.54)	7.36 (7.00-7.53)

TABLE 2. Overall results according to variation outcomes.

Outcome	Arm		p
	NIV	IMV	
Ventilation duration (days) - median (range)	3 (1-26)	10 (0-47)	0.001
ICU hospitalisation stay (days) - median (range)	9 (1-42)	16 (1-91)	0.01
ICU discharge	26 (55.3%)	13 (27.6%)	0.01
Hospital discharge	23 (48.9%)	11 (23.4%)	0.08

By logistic regression, we found that the probability of death in ICU was higher in the patients treated with IMV performed before 1996 (OR=10.86; 95% CI: 2.75-42.80; p=0.001) and in leucopenic patients (OR=6.38; 95% CI: 1.62-25.09; p=0.008). By the same method, we observed that the probability of death in hospital was also higher in the patients treated with IMV performed before 1996 (OR=7.91; 95% CI: 2.03-30.72; p=0.003) and in leucopenic patients (OR=4.53; 95% CI: 1.16-17.62; p=0.03). The type of tumour, the type of respiratory failure, IMV performed after 1996 and the presence of bone marrow transplantation were not identified as independent prognostic factors.

DISCUSSION

The present case-control study shows that non-invasive ventilation results in two significantly important advantages for cancer patients with respiratory failure : shorter ventilation duration and shorter ICU stay. Hospital and ICU discharge rates are significantly improved only when historical controls before 1996 are used for the invasive mechanical ventilation matched cases.

Our data are consistent with those already published in the haematological literature [5,6]. In his retrospective study, Azoulay et al. [5] found that NIV, ICU admission after 1995 and SAPS II score were significantly favourable independent predictors of 30-day mortality in a series of 237 mechanically-ventilated cancer patients. We have also observed that patients treated with IMV before 1996 also had a significantly poorer survival. Depuydt et al. matched 48 NIV subjects with 48 IMV cases and obtained crude ICU mortality rates of 43.7% and 70.8%, respectively [6]. This difference remained significant after adjustment for matching variables (including period of ICU admission). Although we found comparable rates in the overall population, our results were similar to those reported by Depuydt et al, when the analysis was performed in the subgroup of more contemporary controls. Depuydt [6] performed a retrospective study in a series of 168 consecutive patients with haematological malignancies and acute respiratory failure requiring mechanical ventilation. Accrual started in 1997. He matched 27 patients who received NIV with 52 patients who required IMV and found a crude in-hospital mortality rate of 65.4% in both groups, which is in the same range of the results we obtained when using the more contemporary controls.

Our patient population had a different case-mix, with the majority of patients with a solid tumour, contrary to the two other published case-control studies. Depuydt had only haematological malignancies and Azoulay et al. only a small minority

TABLE 3. Subgroup analyses for ICU discharge.

Subgroup	Arm				p
	NIV		IMV		
	N pts	% discharge	N pts	% discharge	
Solid tumours	29	69	28	28.6	0.02
Haematological malignancies	18	33.3	19	26.3	0.63
Leucopenic patients	10	10.0	10	20.0	1
Non leucopenic patients	37	67.5	37	29.7	0.004
Allo-transplanted patients	9	22.2	9	22.2	1
Non allo-transplanted patients	38	63.1	38	28.9	0.004
Hypoxemic respiratory failure	34	47.0	34	20.6	0.02
Hypercapnic respiratory failure	10	90	10	40.0	0.13
Acute haemodynamic oedema	3	66.6	3	66.6	NA
Matching with controls treated before 1996	26	61.5	26	11.5	0.004
Matching with controls treated since 1996	21	47.6	21	47.9	1

TABLE 4. Subgroups analyses for hospital discharge.

Subgroup	Arm				p
	NIV		IMV		
	N pts	% discharge	N pts	% discharge	
Solid tumours	29	58.6	28	21.4	0.01
Haematological malignancies	18	33.3	19	26.3	0.63
Leucopenic patients	10	10.0	10	20.0	1
Non leucopenic patients	37	59.5	37	24.3	0.002
Allo-transplanted patients	9	22.2	9	22.2	1
Non allo-transplanted patients	38	55.3	38	23.6	0.002
Hypoxemic respiratory failure	34	41.2	34	20.5	0.07
Hypercapnic respiratory failure	10	80.0	10	30.0	0.06
Acute haemodynamic oedema	3	33.3	3	33.3	NA
Matching with controls treated before 1996	26	50.0	26	11.5	0.005
Matching with controls treated since 1996	21	47.6	21	38.1	0.75

of solid tumours (12.5%). Published data on NIV in patients with solid tumours are so far limited : one case of dynamic large airway obstruction associated with lung cancer [11], six cases in each arm of the case-control study by Azoulay et al. [5] and two lung cancer patients who refused intubation [12].

There are also differences in the matched variables. For our study, we used 5 variables (type of cancer, bone marrow or stem cell allotransplantation, leucopenia, SAPS II and reason for ventilation). Azoulay et al. matched for 3 variables (type of cancer, reason for ventilation and period of ICU admission) and Depuydt for one only (SAPS II). We used SAPS II because it was in our experience the most important prognostic factor in cancer patients admitted in ICU [13], leucopenia because it was a pejorative independent prognostic factor in our population when IMV was required [9] and allogeneic transplantation because of the particular poor prognosis in case of respiratory failure [14,15].

A limitation of our study is related to its methodology (case-control with historical controls). We had to use historical controls because the selection of contemporary cases for IMV in our data basis would have been potentially highly biased due to the rapid extensive application of NIV in our practice since the technique became available. The main problem resulting from that approach is related to the improvement of care and results of IMV in general intensive care [16,17] and also in critical care of haemato-oncological patients, as already shown by Azoulay [18]. A better level of evidence would be obtained by performing randomised studies testing NIV versus IMV allowing, in a second time, meta-analyses as available for acute exacerbation of chronic obstructive pulmonary disease [19,20], acute hypoxaemic respiratory failure [21] or weaning strategy [22]. Such a scientific approach is today extremely difficult to be adopted because of the very poor base-line prognosis of cancer patients requiring mechanical ventilation and the encouraging results obtained by NIV in this situation. There is only one relatively small randomised trial available [4], performed in immunosuppressed patients (with a majority of haematological malignancies) with pulmonary infiltrates, fever and acute respiratory failure. The administration of intermittent NIV was shown to result in significantly reduced intubation and mortality rates when compared to conventional care with supplemental oxygen. A randomised trial with a similar design and objective has been conducted in patients undergoing solid organ transplantation [3]. NIV resulted in significant reduction of intubation, length of stay in ICU and ICU mortality (but not hospital mortality). Those studies, as well as the case-control studies already mentioned, and the very significant patients' advantages, such as shorter duration of ventilation support, ICU stay and hospitalisation (confirmed in our own study), have led to the widespread application of NIV, with guidelines recommending NIV as initial mode of ventilation support for this type of patients, even in case of ARDS [23].

CONCLUSIONS

In comparison to IMV, the administration of NIV for respiratory failure in cancer patients is associated with important benefits such as reduction in ventilation support duration and in ICU and hospitalisation stay. The impact on mortality is not evident when patients are matched with more contemporary

controls treated since 1996. The obtained benefits, confirmed by other similar studies, render the performance of randomised trials to obtain a higher level of evidence for recommendations ethically difficult. Further developments of NIV may occur with the use of helmet instead of facial mask [24,25] and with the application of ventilation support in cancer patients with limitations for invasive life-support techniques [26].

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