Premedication for bronchoscopy in older patients: a double-blind comparison of two regimens

M.R. Watts[a],*, R. Geraghty[b], A. Moore[a], J. Saunders[c], C.G. Swift[d]

[a]Clinical Age Assessment Unit, Department of Medicine for the Elderly/Medical Day Ward, Limerick Regional Hospital, University of Limerick, Dooradoyle, Co. Limerick, Ireland
[b]Queen Mary's Sidcup NHS Trust, Sidcup, Kent, UK
[c]Statistical Consulting Unit, University of Limerick, Ireland
[d]Clinical Age Research Unit, Guy's, Kings & St Thomas' School of Medicine, King's College, London, UK

Summary *Introduction*: Older patients are the most prevalent age cohort requiring bronchoscopy. Prior sedation should be offered to improve patient comfort and operator technical ease. Older patients have increased sensitivity to centrally acting drugs increasing the procedural risk. This perceived risk may limit access to bronchoscopy in older patients. There have been no systematic prospective placebo-controlled studies in older patients. We compared a novel premedication regimen-oral temazepam plus nebulised lignocaine (new treatment) to an established regimen of intravenous alfentanyl (control).

Methods: Consecutive patients 75 years and older referred for bronchoscopy were considered. Twenty-five patients were randomly assigned to each group. The primary outcome measure was the lowest oxygen saturation recorded from the administration of IV drugs and for 30 min post-bronchoscopy.

Results: The lowest mean oxygen saturation in the new treatment group was 92.2% (90.3–94.2) and in the control group 91.1% (89.2–93.1). This was not statistically different ($P = 0.370$). There were no adverse events.

Conclusion: This is the largest prospective study to date on an older population undergoing bronchoscopy supporting previous retrospective findings regarding the safety of this procedure. Determined by oxygen saturations there is no difference in safety between premedication regimens comprising oral temazepam/nebulised lignocaine or intravenous alfentanyl.

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Introduction

Flexible fibreoptic bronchoscopy (bronchoscopy) is a well-established and commonly used investigation in medicine. Its use is primarily in the diagnosis and staging of endobronchial neoplasms. Lung cancer remains predominantly a disease of older people, who therefore constitute the major age group requiring bronchoscopy.[1]

Although bronchoscopy remains a safe procedure with a less than 0.3% complication rate,[2] concern is often expressed when an older patient is considered for bronchoscopy.

Sedation is generally considered to be worthwhile to improve patient comfort for what can be an unpleasant procedure.[3] It may also make the

*Corresponding author. Tel.: +353-061482938; fax: +353-61482662.
E-mail address: mwatts@mwhb.ie (M.R. Watts).

procedure easier for the bronchoscopist and the patient more willing to accept further bronchoscopy if required.

Ageing is associated with increased sensitivity to some centrally acting sedative drugs,[4,5] declining lung function[6] and increasing indications for bronchoscopy. It is thus important to establish a premedication regimen that minimizes both risk and discomfort so that access to bronchoscopy is not denied to older people on the basis of inadequate evidence. There is no gold standard regarding the choice of premedication in bronchoscopy, although the benzodiazepines and opioids are the most commonly used.[7]

There have been no prospective systematic comparisons of different premedication regimens in older patients.

Hypothesis

An oral benzodiazepine (temazepam) plus nebulised lignocaine exhibits greater safety (with comparable tolerability) when compared with a parenteral opioid (alfentanyl) in older patients undergoing bronchoscopy.

Methods

Patients and procedures

We performed a prospective double-blind randomised placebo-controlled trial on 50 patients 75 years and over who required bronchoscopy. Consecutive patients referred to the primary investigators bronchoscopy list were considered. All patients had a full history and physical examination as well as a review of the case notes. Patients were excluded if taking any benzodiazepine or opioid, as were patients with a resting oxygen saturation of less than 90% on room air, an abbreviated Mental Test Score of less than 7/10[8] or those with an inability to perform a visual analogue scale.[9] Written consent was obtained.

The study was carried out in three centres. Ethics committee approval was obtained independently in each centre.

All bronchoscopies were performed by the same investigator (MW). The primary endpoint of the study was the lowest oxygen saturation recorded throughout and 30 min post procedure. A sample of 25 patients in each treatment group were sufficient to achieve 80% power at the 5% significance level, assuming, the difference in the average reduction in oxygen saturation of 5% in one group and 7% in the other, with a standard deviation in each group of 2.5%.

Twenty-five patients were randomised to the "new treatment" group, receiving 10 mg oral temazepam 1 h before the procedure, 4 ml of 2% lignocaine nebulised 30 min before, "spray as you go" lignocaine through the working canal and 1–2 ml placebo (0.9% NaCl) IV at T_0 (Fig. 1).

Twenty-five patients were randomised to the "normal treatment" group, receiving a placebo tablet (SAC LAB) 1 h before the procedure, 4 ml placebo (0.9% NaCl) nebulised 30 min before, "spray as you go" lignocaine and 250–500 mcg of IV alfentanyl (BMl < 23, 250 mcg, BMl ⩾ 23, 500 mcg) at T_0 (Fig. 1).

The study was double blind and placebo controlled. All medications of both regimens were matched for tablet and vial size, with original labels obscured. Oral medications and nebulisers were administered by nursing staff. Intravenous mediations were administered by the primary investigator (MW).

All nebulisers were administered using a system22 model supplied by oxygen care.

In both groups, a combination of 2% and 4% lignocaine was used as per the "spray as you go" method through the working canal, the dose determined by the bronchoscopist as per the usual method.

Oxygen saturations were recorded every 15 s from the administration of intravenous drugs, and for 30 min post procedure (using standard pulse oxymetry).

All patients received 2 l of oxygen by nasal prongs, and any additional oxygen was recorded. Spirometry was performed pre- and post-bronchoscopy (using a calibrated Vitallograph spirometer). The procedure was recorded on audiotape and cough indices subsequently calculated. A paroxysm or episode of coughing was given a score of 1. The volume of topical lignocaine used was recorded, cardiac rhythm was monitored and any deviations from base line documented. Visual analogue scales were used to assess patient comfort, willingness to undergo a repeat bronchoscopy and operator assessment of sedation. Patient visual analogue scores were repeated 24 h post bronchoscopy and returned by post.

Statistical analysis

All data were assessed for normality. The significance of normally distributed data was assessed using Student's t-tests, and of non-normally distributed data using the Mann–Whitney U test.
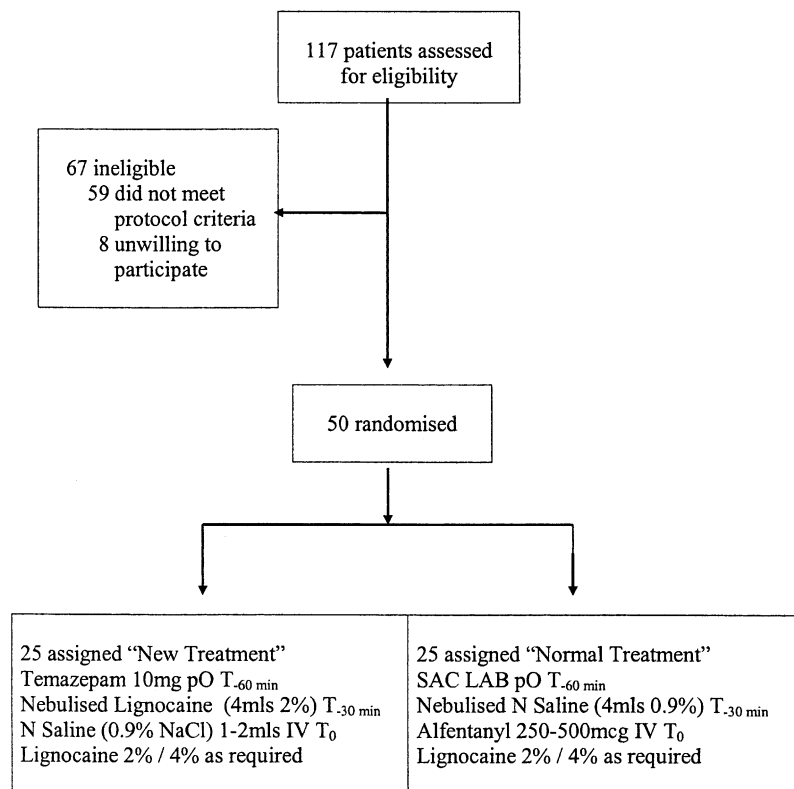
Figure 1 Trial profile.

Table 1

Variable	New treatment (temazepam plus nebulised lignocaine)	Normal treatment (alfentanyl)	P-value
Age (mean ± 95% confidence)	81.6 (79.3/83.8)	80.5 (78.2/82.7)	0.49
Gender (male: female)	12:13	12:13	N/A
Oxygen saturation (%)	92.2 (90.3/94.2)	91.1 (89.2/93.1)	0.416
(mean ± 95% confidence)			0.370

Results

There was no statistically significant difference in age, gender, and base line lung function and resting oxygen saturations on air pre bronchoscopy in both groups (Table 1).The mean age in the new treatment group was 81.6 (95% CI 79.6–83.8) and in the normal treatment group 80.5 (95% CI 78.2–82.7).

Findings at bronchoscopy are summarised in Table 2. The distribution of endobronchial carcinoma and infection were equal in each group. All patients with visible endobronchial lesions had positive biopsies.

The lowest oxygen saturation recorded in the new treatment group was 92.2% (95% CI 90.3–94.2) and 91.1% (95% CI 89.2–93.1) in the normal treatment group (Fig. 2). This variable was close to being normally distributed and thus both para-

metric and non-parametric tests were performed. Neither test revealed a statistically significant difference between the two groups. $P = 0.370$ and 0.416, respectively (Table 1).
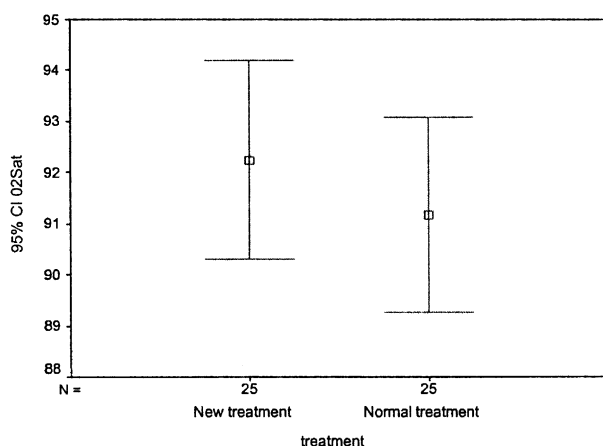
There was no statistically significant difference in lung function in both treatment group's pre and post bronchoscopy (Table 3). There was a statistically significant reduction in coughing paroxysms in the new treatment group (the median cough index of the new treatment group was 4, and 10 in the normal treatment group $P < 0.0005$ (Table 4).

There was a statistically significant lower operator recorded sedation score in the new treatment group, 2.22 (95% CI 1.56–2.87) versus 3.77 (95% CI 2.44–5.10), $P = 0.037$ (Table 4).

There was a statistically significantly lower total dose of topical lignocaine (inclusive of nebuliser)

Table 2 Findings at bronchoscopy.

Diagnostic categories	New treatment (temazepam plus nebulised lignocaine)	Normal treatment (alfentanyl)
Bronchogenic carcinoma (**total**)	11	10
Squamous cell	8	5
Adenocarcinoma	2	4
Small cell	1	1
Infection (**total**)	2	3
Tuberculosis	1	1
Other (**total**)	1	2
Other	4	3
Telangectasia	1	0
Extrinsic compression	3	3
Normal	8	9

Figure 2 Lowest oxygen saturation (%).

used in the new treatment group, median $=294$ mg versus median $=472$ mg in the control group, $P = 0.0005$ (Table 4).

There was no difference in the additional use of oxygen in either group. Patient derived visual analogue scores of discomfort both immediately after the procedure and the next day were significantly lower in the new treatment group ($P = 0.019$), and the next day ($P < 0.0005$) (Table 5). Willingness to undergo a repeat bronchoscopy was significantly greater in the new treatment group, both immediately after ($P = 0.031$) and the next day ($P = 0.006$). 100% of the next day postal questionnaires were returned.

There were no procedure-related adverse events in either group.

Discussion

This is the first prospective double blind randomised controlled study of a specifically elderly group of patients requiring bronchoscopy. There have been no controlled studies that clearly delineate the factors (including age) that makes an individual patient unsuitable for bronchoscopy. Thus the decision to carry out the procedure is made assessing the likelihood of obtaining a diagnosis and a clinical judgement of risk to the patient. The latter is often somewhat subjective, but may include variables such as lung function, oxygen saturation on air and the perceived "general frailty" of a patient. Despite this, bronchoscopy remains an extremely safe procedure with mortality rates around 0.01%, and major complications of 0.3% in a series of about 48,000 procedures.[2]

Chronological age is still sometimes invoked as a deterrent to the carrying out of any procedure with perceived or actual risk attached. To date the majority of studies looking at age with respect to bronchoscopy have been retrospective, simply including older patients in their analysis, rather than studying them specifically. Thus the evidence regarding safety in older patients in terms of prospective placebo-controlled trials is poor if not absent. In view of the well-reported age-associated changes in pharmacological response for some centrally acting agents,[4,5] this is unsatisfactory.

It is generally accepted amongst respiratory physicians that sedation should be offered to patients who are about to undergo bronchoscopy.[3] This not only improves patient comfort but may also make the procedure easier for the bronchoscopist. The choice of sedation however remains variable. Both the opioids and benzodiazepines are widely used and studied. The major difference between the two identified is the well-established retrograde amnesic effect of the benzodiazepines, and the subsequent increased willingness for patients to accept another bronchoscopy.[10]

Table 3 Lung function.

Variable	New treatment (temazepam plus nebulised lignocaine)	Normal treatment (alfentanyl)	P-value
FEV_1 (L) pre-bronch (mean $\pm$ 95% confidence)	1.27 (1.02/1.5)	1.26 (1.1/1.4)	0.938
FVC (L) pre-bronch (mean $\pm$ 95% confidence)	1.73 (1.43/2.04)	1.85 (1.5/2.18)	0.611
FEV_1/FVC (%) Pre-bronch (mean $\pm$ 95% confidence)	71.6 (66.5/77.7)	70.0 (64.1/75.8)	0.664
FEV_1 (L) post-bronch (mean $\pm$ 95% confidence)	1.09 (0.86/1.32)	0.99 (0.83/1.14)	0.445 0.192
FVC (L) post-bronch (mean $\pm$ 95% confidence)	1.49 (1.18/1.80)	1.44 (1.21/1.68)	0.808 0.111
FEV_1/FVC (%) post-bronch (mean $\pm$ 95% confidence)	70.8 (66.6/75.0)	68.5 (63.2/73.8)	0.491 0.850

Table 4

Variable	New treatment (temazepam plus nebulised lignocaine)	Normal treatment (alfentanyl)	P-value
Cough indices (median)	4	10	<0.0005
Sedation (mean $\pm$ 95% confidence)	2.22 (1.56/2.87)	3.77 (2.44/5.10)	0.037
Total dose of lignocaine (mg) (median)	294	472	<0.0005
Additional oxygen vol (l) (median)	0	0	0.934

Table 5 Patient visual analogue scales.

Variable	New treatment (temazepam plus nebulised lignocaine)	Normal treatment (alfentanyl)	P-value
Discomfort T_0 (median)	1.5	4.0	0.019
Discomfort T_0+24 h (median)	1.0	5.0	<0.0005
Another bronchoscopy T_0 (median)	2.0	5.0	0.031
Another bronchoscopy T_0+24 h (median)	1.0	3.0	0.0006

Older patients have a well-documented increased incidence of adverse drug reactions, and specifically an increased sensitivity to centrally acting drugs. This is true of both benzodiazepines[5] and the opioids.[4] Despite these concerns there are no evidence-based guidelines for the sedation of older patients undergoing bronchoscopy.

We chose to compare on oral benzodiazepine plus nebulised lignocaine to an intravenous opioid. Oral temazepam is thought to cause less respiratory compromise and to have a retrograde amnesic effect. Intravenous alfentanyl, a short acting opioid, is thought to be more sedating and thus comfortable for patients, as well as having a significant anti-tussive effect.

The primary endpoint of this study was the lowest oxygen saturation recorded during and 30 min post procedure. Although the alfentanyl group mean oxygen saturation (91.1%) was approximately 1% lower than the temazepam group (92.2%) this did not reach statistical significance. This however may in part relate to the variable measured and thus the design of the study. At and around the 91–92% level, the haemoglobin oxygen disassociation curve begins to decline steeply. Thus small changes in the oxygen saturation can reflect significantly greater changes in the partial pressure of oxygen (PO_2) dissolved directly in the serum and available to supply tissues. Hence the 1.1% difference in oxygen saturation may represent a

clinically significant reduction in the PO_2. However, the logistics of continuous PO_2 measurement are such that this was not undertaken in this study.

Bronchoscopy is associated with a decline in lung function.[2] There was however no statistically significant difference in its decline between our two groups. This is despite there being a statistically significant reduction of operator assessment of sedation in the alfentanyl group. $P = 0.037$ (Table 3).

Lignocaine is the most commonly used local anaesthetic in bronchoscopy. The most common method is "spray as you go", under direct vision with a 2–4% solution. A previous study looking at lung function pre and post bronchoscopy, found the volume of topical lignocaine used was a significant contributor to its decline post bronchoscopy.[11] The use of nebulised lignocaine compared to N Saline prior to bronchoscopy was found by Foster and Hurewitz[12] to significantly reduce the volume of topical lignocaine required in both the upper and lower airways. Despite this, the use of a lignocaine nebuliser pre bronchoscopy is not widely studied. The British Thoracic Society guidelines (2001) recommend the total dose should be limited to 8.2 mg/kg with "extra care" in the elderly, and that 4% nebulised lignocaine can anaesthetize the oropharynx and vocal cords.[3] Thus a 4 ml 2% lignocaine nebuliser was added to the temazepam group (new treatment), and controlled for with a 4 ml 0.9% NaCL nebuliser in the IV alfentanyl group (normal treatment).

This study is the first to show a statistically significant reduction in coughing with nebulised lignocaine when compared to placebo in adults undergoing bronchoscopy (Table 3). Coughing is both unpleasant for patients and may be technically compromising for the bronchoscopist. It is generally accepted that benzodiazepines as a group have little effect on cough apart from their general sedative effects, whereas the opioids are known to have a centrally acting anti-tussive effect. Thus the use of a 4 ml 2% lignocaine nebulised 30 min prior to bronchoscopy may account for the observed reduction in cough in the new treatment group. We have also shown that when nebulised lignocaine was used there was a statistically significant reduction in the mean dose of topically administered lignocaine (294 mg versus 472 mg) $P = 0.0005$. This is supported by the previous findings of Foster and Hurewitz[12] Given that lignocaine is readily absorbed into the circulation during bronchoscopy, the use of a lignocaine nebuliser in older patients undergoing bronchoscopy may reduce the total dose of lignocaine absorbed into the circulation and hence limit adverse events.

Patient assessment of discomfort using a 10 cm visual analogue scale was generally low in both groups (2.42 versus 3.62). There was however a significantly less-reported discomfort in the temazepam/nebulised lignocaine group both immediately and 24 h after bronchoscopy ($P = 0.019$, 0.0005).

Similarly willingness to undergo a repeat procedure was significantly greater in the temazepam/nebulised lignocaine group immediately after the procedure. ($P = 0.031$) This difference was maintained at 24 h ($P = 0.006$).

Conclusion

Although the primary end point of this study did not achieve statistical significance for the difference between regimens, our findings point to the overall superiority for use in older patients of a premedication of oral temazepam/nebulised lignocaine when compared to intravenous alfentanyl in older patients undergoing bronchoscopy. There were clear advantages in terms of patient assessment of comfort, willingness to undergo a repeat bronchoscopy, the objective measurement of coughing and the topical dose of lignocaine used.

This study also supports previous reports confirming the safety of fibreoptic bronchoscopy in older patients. Although the numbers in this study were not large enough to make an overall statement about safety, it does explore further ways in which risk might be minimized.

Within the combined regimen used our findings also suggest advantages in the use of 4 ml 2% lignocaine nebulised 30 min prior to bronchoscopy. By reducing the total dose of lignocaine required systemic absorption and thus potential adverse effects may be minimised. Equally cough and patient comfort appear to be improved. This may be applicable to all adult patients.

This study was not however specifically designed to look at the effect of a nebulised lignocaine alone.

Finally this study did not have a "no sedation" group. Although the BTS recommend sedation,[3] there is often the expressed view amongst bronchoscopists that older patients in particular seem to tolerate bronchoscopy better than younger patients. Despite there being no evidence for this view in the literature, it may be an area worthy of further study.

Equally many centres prefer benzodiazepines as their intravenous agent of choice, particularly since the advent of a specific antagonist (flumazenil). This is also worthy of further study.

Finally given the age profile of patients under-going bronchoscopy, there remains a dearth of evidence in the literature regarding the influence of age on selection criteria and premedication choice. This is an area worthy of further prospective investigation. Our experience in this study suggests there is no practical reason why this and other necessary related research should not be carried out in the relevant patient population.

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