**ARTICLE TITLE:**

**Sedation with remifentanil *versus* propofol for flexible bronchoscopy: A randomised controlled trial.**

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**Materials and methods**

***Study design and setting***

This was a single-centre, randomised controlled study comparing intravenous sedation with propofol TCI vs. remifentanil TCI during flexible bronchoscopy conducted at Saint Louis Hospital (Paris, France) between July 2013 and April 2017. After Institutional Review Board approval (Ethics Review Committee of Saint Louis Hospital, protocol number 090803), trial registration as CT 2011-005175-17 and written informed consent from all study patients, patients were randomised to propofol or remifentanil TCI groups. The study was registered prior to patients enrollment at clinicaltrials.gov (No.NCT01872754, Principal investigator: Véronique J Maurel, MD, Date of registration: June 7, 2013), and the manuscript adheres to the applicable CONSORT guidelines.

***Participants***

The inclusion criteria were patients ≥ 18 years old scheduled for flexible bronchoscopy under intravenous sedation and affiliated with social security. Exclusion criteria were pregnancy, BMI >30 kg.m-2, known allergy to the drugs used, indication to perform anaesthesia under tracheal intubation (*e.g.,* diabetes with dysautonomia, symptomatic gastrooesophageal reflux or hiatal hernia), severe hypoxaemia (*i.e*., SpO2<90%), intracranial hypertension, uncontrolled intermittent asthma or cirrhosis Child’s B or C.

***Study Protocol***

Participants were randomised by an internet/computer-generated randomization (Clean WEB® Copyright ©2018 Telemedicine Technologies, Boulogne-Billancourt, France. https://cleanweb.aphp.fr) to the propofol or remifentanil group, stratified by bronchoscopist’s experience and level of anxiety. Eight senior bronchoscopists participed. Patients evaluated their anxiety using a visual analogue scale (VAS) (0: absence of anxiety to 100: maximum anxiety) when arriving in the operating room. A patient was considered anxious if the VAS value was above twenty.

Patients and bronchoscopists were blinded to the drug used.The anaesthetist who administered the sedation was aware of the product used. Five sprays of nebulised lidocaine, 5 mg.ml-1, were applied in each nasal cavity before the procedure. The fibroscopy was introduced by the nasal route.

 The pulmonologist could add instillations of 2 mg.ml-1 lidocaine during the bronchoscopy on demand. TCI effect-site concentration for propofol or remifentanil was achieved using the Orchestra Base Primea® (Fresenius Vial) using the Schnider or Minto pharmacokinetic model, respectively.(9) Syringes of 1% propofol or remifentanil (50 µg.ml-1) were loaded onto the base Base Primea®. The initial targets were 2.5 µg.ml-1 in the propofol group and 4 ng.ml-1 in the remifentanil group. The TCI was adjusted, every minute, by increments or decrements of 0.5 µg.ml-1 for the propofol group and 1 ng.ml-1 for the remifentanil group until the desired level of sedation was reached. All adjustments to the target site-specific concentrations were standardised (Supplemental Table1). In the remifentanil group, a sedative injection of 0.2 mg.kg-1 of propofol was systematically administered thirty to sixty seconds before the introduction of the fibroscope. The demographic and clinical characteristics were collected before intervention. The vital parameters included the following: SpO2, heart rate, respiratory frequency, blood pressure, EtCO2 (end-tidal CO2), and the Observer’s Assessment of Alertness / Sedation (OAA/S) Scale were collected every minute. EtCO2 was collected by a mask combining oxygen administration with Co2 aspiration.

 The procedure was audio-recorded. The recordings were outsourced and analysed by an anaesthesiologist blinded to the study arm. Prolonged cough episodes were estimated in terms of duration, number and occurrence. Bronchoscopist and patient satisfaction was assessed with a questionnaire. Each item of the questionnaire (items on procedure quality and sedation quality for the bronchoscopist, and items related to fibroscopy tolerance, fibroscopy discomfort and acceptability of the procedure for the patient) was assessed using a Likert scale. There were three different Likert scales (a, b or c). For each question, there were five possible answers, and each answer was rated on five points. For the bronchoscopist, the assessment was performed after the procedure and for the patient just before leaving the post anaesthesia care unit.

***Assessments***

The primary endpoint was the total duration of prolonged cough episodes by subject. A prolonged cough episode was defined by a cough for at least 10 s during the procedure.

The secondary outcomes were as follows: number of prolonged cough episodes by subject, occurrence of at least one episode of prolonged cough, patients and bronchoscopists’ satisfaction, number of adverse events with bronchoscopy interruption, total dose of 2 mg.ml-1- lidocaine instilled by the bronchoscopist during the procedure, total duration of the procedure, total number of target changes (increment and decrements) to achieve effective target concentration and the reasons for these modifications, and the total dose of remifentanil and propofol administered, adverse events (*i.e.,* occurrence of at least one episode of hypoxaemia, occurrence of at least one episode of bradycardia, occurrence of at least one episode of bradypnoea, occurrence of at least one episode of hypotension, occurrence of at least one episode of nausea or/and vomiting, patients with at least one episode of level of sedation ≤ 1 using the responsiveness part the Observer’s Assessment of Alertness/Sedation Scale in Supplemental, occurrence of at least one disappearance of the capnography curve, during the fibroscopy).

***Statistical analysis and sample size*** A preliminary study showed that episodes of prolonged cough (>10 s) were present in 76% of patients sedated with propofol vs. 32% of patients sedated with remifentanil. We decided to include 35 patients per group to detect a 35% absolute risk difference between the 2 groups using Fisher’s exact probability test. The regulatory authorities (CPP 12/26/2012, protocol number 090803) required consideration of the total duration of prolonged cough episodes rather than the percentage of patients with prolonged episodes. We decided to keep the same sample size since it provided power > 85% to detect a large effect size according to Cohen’s criteria (calculation was done using the methods proposed by Noether for power calculation for non-parametric statistics). The analyses were conducted with the intention to treat. Quantitative data were analysed by the Mann-Whitney test. The results are expressed as the median [IQR]. Qualitative data were analysed by the Mantel-Haentzel test. The homogeneity of the odds ratio between strata (*e.g*., the existence of a particular level of anxiety) was tested by the Breslow-Day method. Two-sided *P*-values of < 0.05 were considered significant. Data analysis was performed using the software SAS 9.2® (SAS Institute Inc™, Cary, NC, USA).

Propofol group (n = 31)

Allocated to intervention (n=31)

Lost to follow-up (n=0)

Analysed (n=31)

Wrongly included (n=1) :
- presence of non-inclusion criteria

Inclusion (n=71)

Remifentanil group (n = 39)

Allocated to intervention (n=39)

Lost to follow-up (n=0)

Analysed (n=39)

Randomized (n=70)

Anxious

(n = 19)

No anxious

(n = 12)

Anxious

(n = 23)

No anxious

(n = 16)

Excluded (n=179)

 - refusal of the patient to participate

- presence of non-inclusion criteria

 - investigators not available

Patients screened for flexible bronschoscopy (n=250)

*Fig.1-CONSORT diagram demonstrating the flow of participants in the study.*

**TABLE 1** Baseline characteristics of the study population. Values are mean (SD), median (IQR[range]) or number (proportion).

|  |  |  |
| --- | --- | --- |
| **Characteristics** | **Propofol group*****(n=*31*)*** | **Remifentanil group*****(n=*39*)*** |
| **Age years** | 52.4±15.7 | 50.1±14.1 |
| **Sex, male**, n (%) | 12 (39) | 16 (41) |
| Height, cm | 167.8±8.85 | 168.7± 8.26 |
| Weight, kg | 66.9±13.3 | 65.15±11.5 |
| **ASA physical status** - n (%) |  |  |
| I |  | 1 (3) | 3(8) |
| II |  | 21 (68) | 26 (67) |
| III |  | 9 (29) | 10 (26) |
| **AVS**, mm | 40 [10-60] | 35 [10-50] |
| No anxious (AVS≤20), n (%)  | 12 (39) | 16 (41) |
|  Anxious (AVS>20), n (%)  |  | 19 (61) | 23 (59) |
| **medical treatment**, n (%) |  |  |
| Morphine  |  | 1 (3) | 1 (3) |
| Psychotropic drugs |  | 3 (10) | 5 (13) |
| **Medical history**, n (%) |  |  |  |
| cardiovascular diseases |  | 12 (39) | 13 (33) |
| respiratory diseases |  | 6 (19) | 14 (36) |
| cancer |  | 12 (39) | 14 (36) |
| Haematology diseases |  | 8 (26) | 11 (28) |
| **Interventions realized**, n (%) |  |  |
|  BAL |  | 20 (65) | 23 (59) |
|  Biopsies |  | 11 (35) | 15 (38) |
| **Hb**, g.l-1 |  |

|  |  |
| --- | --- |
|  | 130 [117-142] |

 | 130 [117-142] |
| **Blood platelets**, 1000.mm-3 |  | 233 [173-301] | 249 [195-298] |
| **PT**, % |   | 97 [87-102] | 96 [91-101] |
| **aPTT**, seconds |  | 34 [30-36] | 35 [31-36] |
| **EtCO2** collected before anesthesia, mmHg |  | 26 [22-32] | 26 [23-30] |
| Abbreviations: AVS, analogue visual scale; Hb, haemoglobin; BAL, bronchoalveolar lavage; PT, prothrombin time; aPTT, activated partial thromboplastin time; EtCO2, end-tidal CO2. There were no statistical differences between the group. |

**TABLE 2** Adaptation doses of remifentanil and propofol depending on the patient's response.

|  |  |  |
| --- | --- | --- |
| **Data** | **Cut-off** | **Action** |
| **Hr** | < 55/mn | Decrease\* |
|  | < 50/mn  | Decrease of 50 % in dosage |
| **SBP/DBP** | < 95/52 mmHg or decrease of 20 % if high blood pressure | Decrease\* |
| **SBP/DBP** | < 90/50 mmHg or decrease of 30 % if high blood pressure | Decrease of 50 % in dosage |
| **RF** | < 10 /min or break > 10 s | Decrease\*  |
|  | < 8 /min or break > 15 s | Decrease of 50 % in dosage |
| **SpO2** | Decrease more 3 points  | Decrease\*  |
|  | Decrease more 5 points  | Decrease of 50 % in dosage |
|  | Decrease more 10 points | Stop examen |
| **OAA/S scale** | 2 | Decrease\*  |
|  | 1 | Decrease of 50 % in dosage |
| **discomfort** | Avoidance of the bronchoscopy | Increase\* |
|  | Prolonged cough > 10 s | Increase\*  |

\* Decrease and increase were of 1 ng.ml-1 for remifentanil or 0,5 µg.ml-1 for propofol relative to the previous value.

Abbreviations: HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; RF, respiratory frequency; OAA/S, observer’s assessment of alertness/sedation.

**TABLE 3** Observer’s Assement of Alertness/Sedation Scale (Responsiveness Part).

|  |  |
| --- | --- |
| Responsiveness | Score |
| Responds readily to name spoken in normal tone | 5 |
| Lethargic response to name spoken in normal tone | 4 |
| Responds only after name is called loudly and/or repeatedly | 3 |
| Responds only after mild prodding or shaking | 2 |
| Does not respond to mild prodding or shaking | 1 |

**TABLE 4** Evaluation of cough. Values are median (IQR[range]) or number (proportion).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Propofol****group*****(n=*31*)*** | **Remifentanil****group*****(n=*39*)*** | **OR****(95%CI)** | ***P*  value** |
|  |  |  |  |  |
| **Total duration of prolonged cough episodes**, seconds | 50 [12-138] | 13 [0-70] |  | 0.049 |
| **Secondary outcomes** |  |  |  |  |
|  Number of patients who had at least one episode of prolonged cough, n (%) | 22 (71%) | 24 (62%) | 0.65 (95%: 0.23 to 1.78) | 0.403 |
|  Number of prolonged cough episodes per subject | 2 [0-3] | 1 [0-2] |  | 0.258 |

**TABLE 5** Adverse Events Noted in Study Subjects. Values are median (IQR[range]) or number (proportion).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  **Adverse events, n (%):** | **Propofol****Group** ***(n=*31*)*** | **Remifentanil****Group**  ***(n=*39*)*** |  **OR** **(95% CI)** | ***P*  Value** |
| Oxygen Desaturation | 15 (48%) | 21 (55%) | 1.29 (95%: 0.50 to 3.36) | 0.599 |
| Bradycardia | 1 (3%) | 7 (18%) | 5.8 (95%: 0.75 to 44.98) | 0.054 |
| Bradypnea | 7 (23%) | 16 (41%) | 2.44 (95%: 0.82 to 7.25) | 0.108 |
| Hypotension | 4 (13%) | 8 (21%) | 1.71 (95%: 0.47 to 6.21) | 0.416 |
| Nausea or/and vomiting | 1 (3%) | 0 (0%) | 0.00- | 0.271 |
| Coma | 1 (3%) | 1 (3%) | 0.76 (95%: 0.05 to 11.45) | 0.841 |
| Disappearance of the capnography curve | 1 (3%) | 3 (8%) | 2.48 (95%: 0.23 to 26.10) | 0.444 |
| Minimal EtCO2, mmHg | 12 [10-15] | 13 [10-18] |  | 0.514 |
| Maximal EtCO2, mmHg | 29 [25-32] | 31 [26-35] |  | 0.162 |
| Abbreviations: OR, odds ratio; EtCO2, end-tidal CO2.  Definitions: Oxygen desaturation was defined by a reduction in at least three points of the saturation pulsed in oxygen (SpO2) compared with the value taken in ambient air. Bradycardia was defined by a heart rate (HR) lower than 55 beats per minute. Bradypnoea was defined by a respiratory frequency (RF) lower than eight per minute. Hypotension was defined by a systolic blood pressure (SBP) lower than 90 mmHg or a diastolic blood pressure (DBP) lower than 50 mmHg or a reduction in 30% of the blood pressure if an arterial high blood pressure existed before. Coma was documented by Observer's Assessment of Alertness / Sedation (OAA/S) Scale lower or equal to one. Minimal and maximal EtCO2 were collected during the fibroscopy. The Breslow-Day test was not significant for odds ratios. |

**TABLE 6** Satisfaction of pulmonologists and patients. Values are median (IQR[range]).

|  |  |  |  |
| --- | --- | --- | --- |
| **Satisfaction score** | **Propofol****group*****(n=*31*)*** | **Remifentanil****group*****(n=*39*)*** | **P****value** |
| **Satisfaction score of pulmonologists (/30 points):** | 23 [18-27] | 27 [23-30] | 0.002 |
|  **Score on procedure quality (/15 points), Likert c:** | 12 [10-14] | 13 [11-15] | 0.066 |
| - visualization of the bronchial tree?  | 4 [4-5] | 5 [4-5] | 0.123 |
| - efficiency of the examination?  | 4 [3-5] | 4 [4-5] | 0.431 |
| - comfort of the progression of the fibroscopy?  | 4 [3-5] | 4 [4-5] | 0.022 |
|  **Score on sedation quality (/15 points), Likert a:** | 11 [7-13] | 14 [11-15] | <0.001 |
| - had any interference with the patient's movements?  | 3 [1-4] | 5 [4-5] | <0.001 |
| - had any interference related to the patient's cough?  | 3 [1-4] | 3 [3-5] | 0.001 |
| - had any interference related to the interpositions of the anaesthetist?  | 5 [4-5] | 5 [5-5] | 0.267 |
| **Satisfaction score of patients (/35 points):** | 33 [31-35] | 28 [25-30] | <0.001 |
|  **Score related to fibroscopy tolerance (/15 points), Likert a:** | 15 [14-15] | 10 [9-13] | <0.001 |
| - was this procedure painful?  | 5 [5-5] | 5 [5-5] | 0.749 |
| - did you remember the exam?  | 5 [5-5] | 1 [1-3] | <0.001 |
| - did you cough during the exam? | 5 [5-5] | 4 [3-5] | <0.001 |
|  **Score related to fibroscopy discomfort (/15 points), Likert a:** | 14 [13-15] | 13 [11-14] | 0.011 |
| - was there any discomfort during local anaesthesia?  | 4 [3-5] | 4 [3-5] | 0.477 |
| - was there any discomfort during the introduction of the fiberscope? | 5 [5-5] | 5 [4-5] | 0.018 |
| - was there any discomfort during exploration of the tracheobronchial tree?  | 5 [5-5] | 5 [4-5] | 0.046 |
|  **Score on the acceptability of the procedure (/5 points), Likert b:**  | 5 [5-5] | 5 [4-5] | 0.146 |
| Would you be ready to start the exam again if necessary?  | 5 [5-5] | 5 [4-5] | 0.146 |

Number of points corresponding to the answer to the question,

**Likert scale a,** 1 point: a lot/very, 2 points: moderately, 3 points: a little, 4 points: a little bit, 5 points: not at all; **Likert scale b**, 1 point: absolutely not, 2 points: probably not, 3 points: I do not know, 4 points: probably, 5 points: of course; **Likert scale c,** 1 point: nothing, 2 points: bad, 3 points: I do not know, 4 points: good, 5 points: excellent