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A Randomized Trial of 1% vs 2% Lignocaine by the Spray-as-You-Go Technique for Topical Anesthesia During Flexible Bronchoscopy

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BACKGROUND: The optimal concentration of lignocaine to be used during flexible bronchoscopy (FB) remains unknown. This randomized controlled trial compared the efficacy and safety of 1% and 2% lignocaine solution for topical anesthesia during FB.

METHODS: Consecutive patients were randomized to receive either 1% or 2% lignocaine solution through the bronchoscope by the "spray-as-you-go" technique. The primary outcome of the study was the assessment of cough by the operator and the patient using the visual analog scale (VAS) and pain assessment using the faces pain rating scale. The secondary outcomes included total lignocaine dose, oxygenation status, adverse reactions related to lignocaine, and others.

RESULTS: Five hundred patients were randomized (median age, 51 years; 71% men) 1:1 to either group. The median operator VAS score for cough was significantly higher (25 vs 21, $P = .015$) in the 1% group; however, the patient VAS score was not significantly different (32 vs 27, $P = .065$). The pain rating was similar between the two groups. The median cumulative dose of lignocaine was significantly higher in the 2% group (397 mg vs 312 mg, $P = .0001$; 7.1 mg/kg vs 5.7 mg/kg, $P = .0001$). About 28% of patients in the 2% group exceeded the maximum recommended dose (> 8.2 mg/kg) of lignocaine. No adverse event related to lignocaine overdose was seen in either group.

CONCLUSIONS: One percent lignocaine was found to be as effective as 2% solution for topical anesthesia during FB, albeit at a significantly lower dose as the latter. Thus, 1% lignocaine should be the preferred concentration for topical anesthesia during FB.

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ABBREVIATIONS: EBB = endobronchial biopsy; FB = flexible bronchoscopy; RCT = randomized controlled trial; TBLB = transbronchial lung biopsy; TBNA = transbronchial needle aspiration; VAS = visual analog scale

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Flexible bronchoscopy (FB) is a widely used procedure for the diagnosis and treatment of a variety of bronchopulmonary disorders because of patient comfort, low rate of complications, and lack of requirement of general anesthesia.[1] Most patients tolerate the procedure well although cough is reported to be an extremely distressing symptom.[2] It is likely that the acceptance of bronchoscopy would be significantly improved with control of cough. A combination of midazolam and hydrocodone has been shown to significantly reduce cough during FB, especially when invasive diagnostic procedures are performed.[3] However, in several centers including ours, due to logistics, sedation is not routinely used during basic diagnostic bronchoscopy; procedures such as BAL, endobronchial biopsy (EBB), and transbronchial lung biopsy (TBLB) are performed under topical anesthesia.

Lignocaine is the most common local anesthetic used during FB because of its quick onset, short duration of action, and lesser toxicity compared with other agents.[4] The use of topical lignocaine during FB has been shown to improve patient's tolerance and satisfaction of the procedure.[5,6] Furthermore, it has been demonstrated that nebulized lignocaine can reduce the need for supplemental topical anesthesia, administered as injection through the bronchoscope.[7,8] The optimal concentration of lignocaine as topical anesthesia, however, remains speculative, and 1% and 2% concentrations of lignocaine solutions are commonly used. The British Thoracic Society guidelines recommend the use of 1% lignocaine while the American College of Chest Physicians (CHEST) consensus statement endorses a wide range of lignocaine concentrations (1%-10%) that have been found to be effective without advocating any particular value.[9,10]

There is little data on the efficacy of lower concentrations (1%-2%) of lignocaine.[11] It is important that the superiority of a particular concentration be ascertained, as effectiveness of lower concentrations would allow the use of higher volumes with lesser chances of complications. In this randomized controlled trial (RCT), we report the efficacy and safety of 1% vs 2% lignocaine for topical anesthesia in patients undergoing FB.

Materials and Methods

Setting

This was an investigator-initiated, single-center, randomized double-blind trial conducted in the bronchoscopy suite of this institute between May and November 2014. The study protocol was approved by the Ethics Review Committee (Ref. No. NK/1473/Res/687), and written informed consent was obtained from all the patients. As a protocol in our bronchoscopy suite, patients undergoing BAL, EBB, and TBLB are not routinely sedated, and bronchoscopy is performed under topical anesthesia. Patients undergoing other procedures such as conventional transbronchial needle aspiration (TBNA), endobronchial ultrasonography-guided TBNA, and other interventions are routinely sedated with midazolam and pentazocine.

Patients

Patients were eligible for inclusion into the study if they met all of the following criteria: (1) indication for flexible bronchoscopy, (2) age group of 12 to 90 years, and (3) hemodynamic stability (defined as systolic BP $>$ 100 mm Hg and $<$ 180 mm Hg). Patients with any of the following were excluded: (1) pregnancy, (2) hypoxemia (oxygen saturation [by pulse oximetry] $<$ 92% with F_{IO_2} of 0.3), (3) patients undergoing TBNA and other interventions, and (4) failure to provide informed consent.

Randomization

Patients were randomized in 1:1 ratio to receive either 1% or 2% lignocaine solution. The randomization sequence was computer-generated, and the assignments were placed in sealed opaque envelopes. Both the patient and the bronchoscopist were blinded to the concentration of lignocaine solution used for the procedure.

Study Protocol

Demographic profile including age, sex, height, weight, smoking history, BMI, and the type of procedure performed (airway inspection, BAL, EBB, TBLB) was recorded for all patients. Patients in both the groups were prepared in a similar fashion except for the concentration of lignocaine used. All patients were kept fasting overnight. The patients were nebulized with 2.5 mL of 4% lignocaine (Lox, 42.7 mg/mL; Neon Laboratories Ltd) for 15 min prior to the procedure. Lignocaine spray (10%, Lox, 100 mg/mL; Neon Laboratories Ltd) was sprayed twice (10 mg/puff) over the oropharynx. Approximately 5 mL of lignocaine gel (2%; Neon Laboratories Ltd), equivalent to 100 mg of lignocaine, was administered in the nasal cavity prior to the introduction of the bronchoscope. Patients thereafter received 2-mL aliquots of 1% or 2% lignocaine solution (Wocaine; Wockhardt) delivered through the bronchoscope using the "spray-as-you-go" technique. Four aliquots of 2 mL of lignocaine were administered: one each at the vocal cord, tracheal carina, and in the right and left main bronchus. Extra lignocaine aliquots were given as a "rescue" treatment to suppress cough, at the discretion of the operator. The sum of the standard dose (2.5 mL of 4% nebulized lignocaine [106.75 mg] plus 5 mL of 2% lignocaine gel [100 mg] plus two puffs of 10% lignocaine spray [20 mg] plus 8 mL of 1% [85.2 mg] or 2% [170.4 mg] lignocaine) and rescue dose made up the total dose of lignocaine used. Patients were monitored for any adverse effects related to lignocaine use (like arrhythmia, involuntary movements, convulsions, anaphylaxis, and bronchospasm). Heart rate, respiratory rate, BP, and oxygen saturation (by pulse oximetry) were monitored throughout the procedure.

The bronchoscopist was asked to assess the intensity of the patient's cough during FB using a visual analog scale (VAS) immediately after the procedure. The VAS for cough was rated on a horizontal line, 100 mm in length anchored by "No cough" at one end and "Worst cough" at the other.[12] Once stable, the patients recorded their quantum of cough and pain using the VAS and the faces pain rating scale, respectively. The faces pain rating scale consists of six faces with brief word instructions provided with the scale representing increasing intensity of pain on an ordinal scale from 0 to 5.[13]

Study Outcomes

The primary outcome of the study was patient comfort during the procedure measured by the intensity of cough rated on a VAS by both the operator and the patient and the pain assessment by the patient using the faces pain rating scale. The secondary outcomes included total lignocaine dose; changes in respiratory rate, heart rate and BP, and

oxygenation status following the procedure; and adverse reactions related to lignocaine (arrhythmia, involuntary movements, convulsions, anaphylaxis, and bronchospasm).

Statistical Analysis

Statistical analysis was performed using the commercial statistical package SPSS for MS-Windows, version 22 (IBM Corporation). $P < .05$ was considered as statistically significant. Data are presented in a descriptive fashion as number with percentage or median with interquartile range. χ^2 (or the Fisher exact test) was used to analyze categorical variables and the Mann-Whitney *U* test was used for comparing the numerical data. The change in variables before, during, and after the procedure was analyzed with multiple repeated measure analysis of variance.

Results

During the study period, 500 consecutive patients (250 in each group, 70.6% men) with a median (interquartile range) age of 51 years (40-60) were included in the study (Fig 1). The baseline characteristics including the demographic characteristics, physiologic parameters, and the type of bronchoscopic procedures performed were similar in the two groups (Table 1). Heart rate, respiratory rate, and BP increased after the procedure as compared with baseline in both the study groups. However, the change was not significantly different between the two groups (Table 2).

The median operator VAS score for cough was significantly higher in the 1% group (1% group: 25 vs 2% group: 21; $P = .015$); however, the median patient VAS score for cough was similar between the two groups (Table 3). The faces pain rating score was similar in the two groups (Table 3). The median total dose of lignocaine used was significantly higher in the 2% group (2% group: 397 mg vs 1% group: 312 mg; $P = .0001$). Similarly, the lignocaine dose adjusted for body weight was also significantly higher in the 2% group (Table 3). The number of patients with total administered dose > 8.2 mg/kg lignocaine was also significantly higher in the 2% group (Table 3). Heart rate, respiratory rate, and BP after the procedure were similar in the two groups. No adverse events related to lignocaine such as bronchospasm, arrhythmias, involuntary movements, or convulsions were observed in any patient.

Discussion

The result of this large RCT demonstrates that 1% and 2% concentrations of lignocaine solution are equally effective in anesthetizing the airway. The bronchoscopist-reported VAS scores for cough were higher in the 1% lignocaine group; the difference although statistically significant is unlikely to be clinically relevant as the

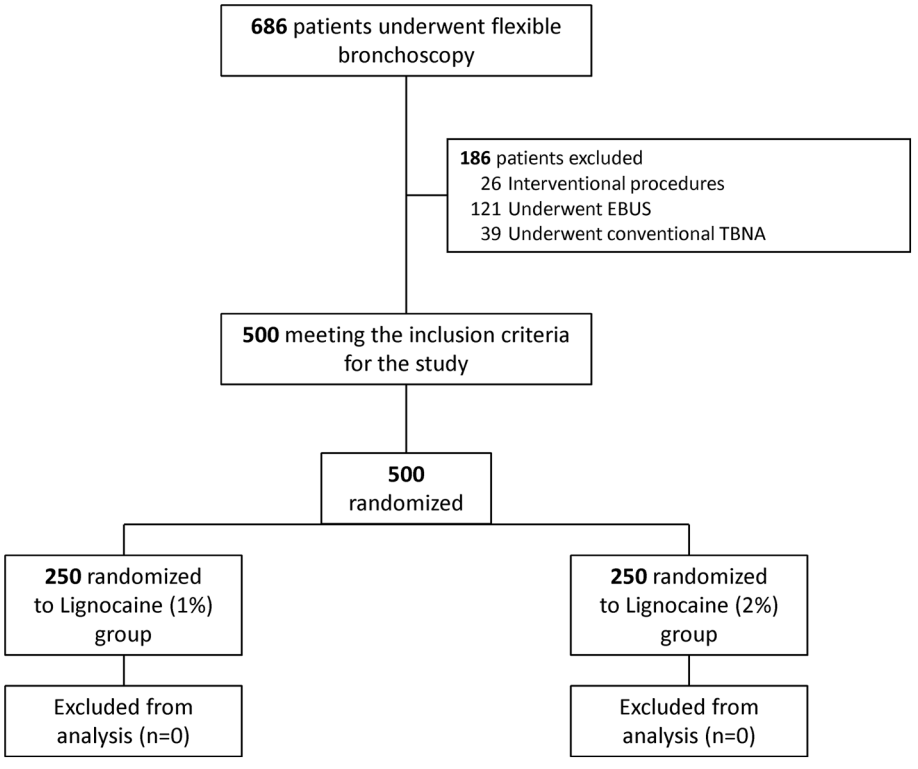

Figure 1 – *CONSORT diagram demonstrating the flow of participants in the study. EBUS = endobronchial ultrasonography; TBNA = transbronchial needle aspiration.*

TABLE 1] Baseline Characteristics of the Study Population

Characteristics	1% Lignocaine (n = 250)	2% Lignocaine (n = 250)	Total (N = 500)	*P* Value
Demographic variables				
Male, No. (%)	177 (70.4)	176 (70.8)	353 (70.6)	.890
Age, y	50 (40-60)	52 (38-61)	51 (40-60)	.710
Height, cm	165 (157-170)	165 (155-170)	165 (156-170)	.873
Weight, kg	55 (49-64)	56 (48-65)	55 (49-65)	.595
BMI, kg/m^2	20.5 (18-23)	20.9 (18-24)	20.8 (18-24)	.540
Current smokers, No. (%)	106 (42.3)	104 (41.8)	210 (42)	.926
Physiologic parameters				
Heart rate, beats/min	98 (87-111)	98 (86-111)	98 (86-111)	.804
Respiratory rate, breaths/min	20 (18-22)	20 (18-22)	20 (18-22)	.340
Oxygen saturation, %	97 (95-98)	97 (95-98)	97 (95-98)	.349
Systolic BP, mm Hg	120 (110-135)	122 (112-137)	121 (112-136)	.136
Diastolic BP, mm Hg	76 (69-83)	76 (70-84)	76 (70-83)	.662
Procedures performed, No. (%)				
BAL	86 (34.4)	82 (32.8)	168 (33.6)	.753
Endobronchial biopsy	90 (36)	86 (34.4)	176 (35.2)	.758
Transbronchial lung biopsy	67 (26.8)	59 (23.6)	126 (25.2)	.440
Airway inspection only	70 (28)	73 (29.2)	143 (28.6)	.724

All values are expressed as median with interquartile range, unless otherwise stated.

median difference of VAS score was merely four points on a scale ranging from 0 to 100. Moreover, the difference was not significant in the patients' own assessment of their cough in the two groups. The pain rating was also not different in the two groups. The cumulative dose in the 1% arm was significantly lower compared with the other group. Thus, 1% lignocaine could achieve topical anesthesia during bronchoscopy as effectively as 2% but at a much lower dose compared with 2% lignocaine.

Most guidelines currently recommend performance of FB under IV sedation.[9,10] However, in our center, due to high patient load and lower doctor-to-patient ratio, basic diagnostic procedures such as BAL, EBB, and TBLB are performed under topical anesthesia without any IV sedation. Although sedation should be used wherever possible,[3,14] local anesthesia can be achieved within 2 min of endotracheal lignocaine application, which blunts the cough reflex effectively,[15] allowing for safe and comfortable performance of FB.[16]

TABLE 2] Serial Physiologic Parameters Measured Before, During, and After FB in the Two Groups

	1% Lignocaine			2% Lignocaine		
Parameters	Baseline	During	After	Baseline	During	After
Heart rate, beats/min	99.0 (18.4)	113.4 (20.7)[a]	110.9 (18.8)[b]	98.6 (17.9)	112.4 (19.9)[a]	107.8 (17.9)[b]
Respiratory rate, breaths/min	19.9 (3.5)	…	22.5 (3.3)[b]	20.2 (3.6)	…	22.4 (3.3)[b]
Systolic BP, mm Hg	122.5 (17.8)	…	124.5 (16.1)[b]	125.1 (16.6)	…	126.6 (15.5)[b]
Diastolic BP, mm Hg	75.5 (10.9)	…	76.1 (10.1)	76.4 (10.2)	…	76.5 (9.8)
Oxygen saturation, %	96.2 (3.2)	96.7 (3.2)	96.3 (2.5)	96.5 (2.8)	96.5 (2.9)	96.3 (2.7)

All values are mean (SD) unless otherwise stated. $P < .05$ was taken as significant. The differences between the means was analyzed using multiple repeated measure analysis of variance with Bonferroni adjustment for multiple comparisons; the within-groups factor was time (baseline, during, and after), and the between-groups factor was the lignocaine groups (1% vs 2%). FB = flexible bronchoscopy.

[a]Value during procedure significantly different from that at baseline within the groups.

[b]Value after procedure significantly different from that at baseline within the groups.

TABLE 3] Primary and Secondary Outcomes of the Study

Outcomes	1% Lignocaine (n = 250)	2% Lignocaine (n = 250)	*P* Value
Primary			
VAS score (cough) for operator	25 (12-51)	21 (9-38)	.015
VAS score (cough) for patient	32 (11-60)	27 (10-50)	.065
Faces pain rating scale	0 (0-2)	0 (0-2)	.883
Secondary			
Total dose of lignocaine, mg	312 (312-312)	397 (397-397)	.0001
Lignocaine dose, mg/kg	5.7 (5.0-6.5)	7.1 (6.1-8.3)	.0001
No. of patients with dose > 8.2 mg/kg, No. (%)	12 (4.8)	70 (28)	.0001
Heart rate after procedure, beats/min	111 (98-123)	108 (96-118)	.054
Respiratory rate after procedure, breaths/min	22 (20-24)	22 (20-24)	.493
Systolic BP after procedure, mm Hg	122 (112-132)	126 (116-134)	.075

All values in median (interquartile range), unless mentioned. VAS = visual analog scale.

Few studies have evaluated the effective lignocaine concentration for topical anesthesia during FB (Table 4).[11,17-19] Of the four, one has been published only as an abstract while three are peer reviewed.[19] Of the three peer-reviewed studies, only a single study was performed in the bronchoscopy suite, while the other two studies were conducted in the operating suite and are, thus, different from the routine practice in the bronchoscopy suite. The results of these studies suggest that 2% is as efficacious as 4% solution while 1% is as effective at 2% lignocaine. The limitation of these studies apart from differing methodologies is the small sample size. The results of our study supplement these studies and confirm that 1% lignocaine solution is as efficacious as 2% but has the added advantage of effectiveness at significantly lower cumulative dose.

These findings are important for routine practice as there are reported cases of death from presumed lignocaine toxicity after FB.[20,21] In fact, 28% of patients in the 2% lignocaine arm of our study exceeded the dose of > 8.2 mg/kg, recommended as the maximum dose by the British Thoracic Society.[22] In another study, the anesthetists used doses of up to 14.8 mg/kg lignocaine by a spray-as-you-go method in a study involving volunteer subjects undergoing awake fiber-optic intubation; some volunteers were reported to have experienced involuntary movements, symptoms that may precede convulsions, which is a sign of lignocaine toxicity.[23] The pharmacokinetics of topical lignocaine during FB are complex and can be influenced by several factors, including the duration and frequency of suctioning.[24] This means that the plasma levels

TABLE 4] Studies Evaluating Different Lignocaine Concentrations for Topical Anesthesia During FB

Study/Year	Nature of the Study	No. of Patients	Concentration of Lignocaine	End Points	Outcome
Mainland et al[17]/2001	Double-blind RCT	96	1% (n = 31) vs 1.5% (n = 16) vs 2% (n = 48)	Nature and duration of cough; requirement of additional supplements	All concentrations and dosages equally effective
Hasmoni et al[11]/2008	Double-blind RCT	61	1% (n = 32) vs 2% (n = 29)	Cough frequency with digital voice recorder; bronchoscopists overall satisfaction	No difference between the two groups
Xue et al[18]/2009	Double-blind RCT	52	2% (n = 26) vs 4% (n = 26)	Faces pain rating scale, 4-point cough severity scale, 3-point tracheal intubation scale	No difference between the two groups
Bansal et al[19]/2011	Double-blind RCT	52	1% (n = 26) vs 2% (n = 26)	VAS, cough severity, and frequency score	No difference between the two groups

RCT = randomized controlled trial. See Table 2 and 3 legends for expansion of other abbreviations.

achieved in an individual patient are often unpredictable.[25-29] However, the propensity would increase with increasing doses of lignocaine used. By using 1% lignocaine, the risk of potential toxicity would be lower although it is still essential to carefully monitor the amount of lignocaine administered during FB. Another important benefit of a lower concentration would be the usage in patients with renal and hepatic dysfunction, as well as in patients with airway inflammation and pediatric age group, as the dose would be minimized.

Finally, our study is not without limitations. There were several factors in our study that could affect the outcomes. These were multiple operators (consultants, fellows), variable duration of bronchoscopy, wide range of indications, and concomitant procedures. However, they were equally distributed between the two groups. The other limitation could be the lack of widespread generalization of our results given the fact that IV sedation was not used while a vast majority of bronchoscopists use sedation. However, lack of sedation can also be regarded as a major strength of the study as it allowed a clear assessment of the cough severity by the patient in contrast to the previous study where the patients were sedated.[11] The other obvious strength of the study is the large sample size.

In conclusion, the results of this study suggest that 1% lignocaine is similar in efficacy to 2% lignocaine for topical anesthesia during FB, at significantly lower doses of lignocaine. Hence, 1% lignocaine should be the preferred concentration for topical anesthesia of the larynx and the tracheobronchial tree during FB.

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