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**Effect of One-Stage versus Two-Stage Palatoplasty on Hypernasality and Fistula Formation in Children with Complete Unilateral Cleft Lip and Palate: A Randomized Controlled Trial**

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**Short running head:** Hypernasality and Fistula Occurrence Following One or Two-stage Palatoplasty

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Statement of financial interest

No financial interest to declare

List of products used in the manuscript

1. Sealed envelope™, Sealed Envelope Ltd, London, UK  
Nasometer-II, 6450 PENTAX Medical, Lincoln Park, NJ, USA

## **Abstract**

### Background

Is one or two-stage palatoplasty more effective preventing fistula formation and hypernasality in patients with complete unilateral cleft lip and palate?

### Methods

This parallel blocked randomized controlled trial included 100 patients with non-syndromic complete unilateral cleft lip and palate with a repaired cleft lip, divided into 2 groups of 50 each. Group A had one-stage palatoplasty at age 12-13 months while group B had two-stage palatoplasty with soft palatoplasty at age 12-13 months and hard palatoplasty at age 24-25 months. Presence of a fistula was tested clinically at 3 years and speech was tested using nasometry and perceptual analyses at 6 years. Group C were the non-cleft controls (n=20, age 6 years) for speech using nasometry. Fistula rates, ratings of hypernasality and nasalance scores were compared between groups A and B. Nasometry recordings of group A and B were compared with control group C.

### Results

There was no difference in fistula rates between groups A and B ( $p=0.409$ ; 95% CI=[0.365...11.9]). Mean nasalance scores of group A showed higher nasalance than group B ( $p=0.006$ , 95CI=[1.16...6.53]). Perceptual analysis showed no difference between groups A and B ( $p=0.837$  and  $p=1.000$ ). When compared to group C, Group A showed higher mean nasalance ( $p=0.837$  and  $p=1.000$ ) while group B showed no difference ( $p=0.088$ , 95% CI=[-0.14...2.02]).

### Conclusion

There was no difference in fistula rates between groups. Nasalance was slightly higher in patients who had one-stage palatoplasty when compared to those that had two-stage palatoplasty, but the difference may not be clinically significant.

## **Introduction**

Although cleft palate repair has significant benefits for the patient's feeding and middle ear function, the primary purpose of cleft palate repair is to help the patient develop normal speech with a functioning velopharyngeal valve.<sup>1-4</sup> Incomplete closure of the velopharyngeal valve during speech, despite the palate repair, causes velopharyngeal insufficiency. In addition, failure to completely close the hard palate can result in a fistula that is large enough to cause nasal regurgitation and speech impairment. Patients with velopharyngeal insufficiency or a large palatal fistula will demonstrate hypernasality and/or nasal air emission during speech<sup>5</sup>. The lack of adequate oral airflow can also cause difficulties in the production of pressure consonant sounds, such as plosives, fricatives, and affricates. As a result, many patients develop active compensatory articulation productions<sup>6,7</sup>.

There are many techniques used by surgeons to repair a cleft palate. However, there is very little agreement between surgeons as to the technique, staging and timing of cleft palate surgery for the best outcomes<sup>8,9,10</sup>. The variations of timing and technique of repairing the cleft palate include early closure of the soft palate followed by closure of the hard palate and lip<sup>11</sup>, simultaneous closure of the cleft lip and palate in a one-stage procedure<sup>12-14</sup>, closure of the cleft lip first followed by the closure of the hard and soft palate in one operation,<sup>15</sup> or soft palate repair followed by delayed hard palate repair<sup>16-19</sup>.

The purpose of this study was to investigate the effect of a one-stage versus two-stage cleft palate repair on the incidence of hypernasality and fistula formation in patients with unilateral complete cleft lip and palate.

## Methods

### *Trial design*

This study was performed at a high volume center that performs more than 700 primary cleft lip and palate surgeries every year. The trial was registered with the ISRCTN registry (ID number ISRCTN17288141). The intake period was from January 1, 2010 to December 31, 2010. The follow-up period lasted until December 2015. The local Ethical Committee approved the research protocol based on the guidelines declared by the local government with regard to . All participants' parents were informed about the study and signed a written informed consent. Reporting of the trial in this paper follows the CONSORT (Consolidated Standards of Reporting Trials) statement<sup>20</sup>.

This study was a parallel blocked randomized trial. Due to the nature of the interventions surgeon and patients could not be blinded to the treatment method. Observers and statistician were blinded for the treatment.

### *Eligibility and randomization*

The inclusion criteria were patients with non-syndromic complete unilateral cleft lip and palate with a previously repaired cleft lip. Exclusion criteria were patients with bilateral cleft lip and palate, isolated cleft palate, younger than 12 months and older than 13 months of age and patients with associated syndromic conditions.

No data from previous studies with comparable outcomes were available, so a formal power calculation was not possible. We estimated that with an intake period of one year, we would be able to include 100 patients, which would be a sufficient number to measure the effect of the surgical procedure on hypernasality. We ensured that there was no loss of patients to follow up by meticulously updating their addresses and telephone numbers.

The surgical interventions and the randomisation procedure were explained to the parent(s) of each eligible patient. If the parents did not agree to be part of the study, the child was

excluded from the trial. After obtaining consent from the patient's parent(s), each patient was randomly assigned to either group A (one-stage palatoplasty) or group B (two-stage palatoplasty). The randomization sequence was generated by a computer program (Sealed envelope™, Sealed Envelope Ltd, London, UK) using blocked randomization in block sizes of 20 in each block. Within each block, participants were randomly assigned numbers by a computerized program to one of the two treatment groups. The randomization was performed by one surgeon who did not perform the surgery (SGR). The surgeon (RRR) was blinded to the randomization process. After assigning the treatment method, each patient's parents were informed of the treatment plan by the surgeon who performed the randomisation (SGR).

### *Interventions*

One surgeon (RRR) performed the palatal surgery on patients in both groups. The Bardach two-flap technique<sup>21</sup> with optimal muscle dissection or levator myoplasty was performed for patients in group A (at age 12-13 months) as a single procedure. The levator myoplasty was performed by relieving the levator muscle from the posterior border of the hard palate and repositioning it medially to be sutured to the contralateral levator veli palatini muscle. The tensor veli palatini muscle was not disturbed from its attachment (Figure 1a-d). We did not dissect the tensor veli palatini muscle in the soft palate. In non-cleft palates, the tensor veli palatini is inserted into the palatine aponeurosis and the surface behind the transverse ridge on the horizontal part of the palatine bone<sup>22,23</sup>. In patients with cleft palate the tensor veli palatini muscle is also attached in the same area and, therefore, does not require any dissection.

The patients in group B had soft palatoplasty with levator myoplasty (at 12-13 months of age) and two flap hard palatoplasty (at 24-25 months of age) as a separate procedure.

### *Presence of fistulas*

Patients in group A and B were recalled at age 3 years to clinically examine them for the presence of fistulae. A single examiner (RRR) performed the examination to elicit the presence or absence of fistula. The examiner was blinded as to whether the patient had had a one-stage or two-stage cleft palate repair. Fistula occurrence was tested visually as the first stage. If there was no visual sign of a fistula, history of nasal regurgitation was elicited. If the parent(s) gave a history of nasal regurgitation, a blunt periodontal probe was used to confirm a fistula in the hard palate. If a hard palate fistula was present, the fistula was repaired at this stage.

### *Speech analysis*

Patients in group A and B were recalled at age 6 to test for hypernasality in speech. Two methods were used to test hypernasality: nasometry and perceptual analysis.

Nasometry is a method of measuring the acoustic correlates of velopharyngeal function during speech<sup>24</sup>. A nasometer captures data regarding acoustic energy from both the nasal (N) cavity and the oral (O) cavity during speech and then calculates the average ratio of nasal over total (nasal plus oral) acoustic energy. This ratio is converted to a percentage value and is called the nasalance score.

Using the Nasometer-II, 6450 (PENTAX Medical, Lincoln Park, NJ, USA), each patient was tested at age 6 by two speech-language pathologists (AC, SK). Each patient was retested after one hour by the same two speech-language pathologists. The passages that were used were from a revised version of the Simplified Nasometric Assessment Procedures Test- Revised (SNAP Test-R), developed by MacKay-Kummer in 2005<sup>6</sup>. The SNAP Test-R has three subtests: prolonged sounds, picture-cued sentences, and reading passages. In this study the picture-cued and reading passages subtests were tested. The language used to perform this

test was English. Children were asked to repeat the stimulus after the examiner. The nasometer was activated only when the patient was speaking.

Perceptual analysis was done using a standardized protocol for reporting speech outcomes in individuals with cleft lip and palate, developed by Henningsson et. al. in 2008<sup>25</sup>. A standardized test in Telugu, the local language, known as the Telugu Test of Articulation and Phonology (TTAP), developed by Vasanta in 1990<sup>26</sup>, was used as one of the stimuli to determine hypernasality.

The collected speech samples were presented in a random order to two qualified speech-language pathologists (AC, SK) who were blinded to the subject's identity and treatment. These samples were analyzed and scored independently to determine the presence/absence and/or severity of five speech parameters. An overall rating of hypernasality for each speech sample at the word and sentence level for one hundred single words and ten sentences of TTAP respectively were rated using a 4-point rating scale, with 0 being the best and 3 being the poorest outcome.

If hypernasality was found to be present, secondary procedures were performed to lengthen the soft palate. If no hypernasality was elicited speech therapy was continued.

#### *Control group*

A control group (group C) was assembled with 20 children, aged six years, with no history of cleft lip and/or cleft palate. As we assumed that the control group would show less variability, a smaller group as compared to the experimental groups was thought to be sufficient. All subjects in this group underwent nasometry and perceptual analysis using the same standards as those used for groups A and B.

#### *Statistical methods*

Odds Ratios were used to compare fistula rates between groups A and B.

Reliability of the testing method was performed between the test and retest nasometry outcomes and calculated by the Pearson Correlation coefficient. The duplicate measurement error (DME) was calculated as the mean standard deviation of the difference between measurement and remeasurement divided by  $\sqrt{2}$ . The kappa statistic was used to test the reliability of the perceptual outcomes.

For all nasometry and perceptual analysis outcomes measured in the comparisons between experimental groups (A and B) and control groups (C), mean values of the test-retest scores were used.

Independent samples t-test was used to assess the differences between the nasometry outcomes of group A and B. For perceptual outcomes chi-square tests were used to test the differences.

The nasometry scores between the experimental groups A and B were compared to control group C using independent samples t-tests.

The relationship between nasometry and perceptual outcomes was tested using ANOVA.

## **Results**

The flow of participants through each stage of the study is detailed in Figure 2. All patients in group A were operated at age 12-13 months. All patients in group B had soft palatoplasty done at age 12-13 months and hard palatoplasty at age 24-25 months. No patients were lost to follow up

In group A, 15 out of 50 children were female (30%). In group B, 20 out of 50 children were female (40%). Because none of the analyses showed gender to be of any significance, all results are presented irrespective of gender.

### *Presence of fistulas*

In group A, 4 children had clinically evident fistulas, whereas in group B, 2 children had fistulas. The odds ratio for this was 2.1, which was not significant ( $p=0.409$ ; 95% CI=[0.365...11.9]).

### *Speech Analysis*

#### *Test Retest Analysis*

The results for the test-retest reliability for the SNAP Test-R are shown in Table 1. A reliability coefficient of more than 0.8, a low duplicate measurement error (DME) and a  $p$ -value above 0.05 meant that the testing protocol was reliable. There was a clear tendency for the second measurements to differ from the initial measurements. In all testing parameters, the second measurement was lower, this being statistically significant for four out of five outcomes. The differences between the first and second measurement ranged from 0.37 to 1.55%, which were small enough to indicate that the differences were within a range to consider them reliable.

For the perceptual analysis of hypernasality in “single words” and “sentences,” the kappa values were 0.799 and 0.765 indicating very good reproducibility of these outcomes.

#### *Speech outcomes between one and two-stage palatoplasty*

Table 2 shows the differences between the experimental groups with regard to the nasalance scores. The mean nasalance score for group A was 20.61% (sd 9.23) and the mean nasalance for group B was 16.77% (sd 2.15). The difference between the groups reached statistical significance ( $p=0.006$ , 95% CI=[1.16...6.53]).

Table 3 shows that for the perceptual analysis of resonance, group A had slightly better results (18 patients with hypernasality on single words versus 20 patients in Group B), but the difference was not statistically significant ( $p=0.837$  and  $p=1.000$  for single words and sentences respectively).

### *Comparing experimental groups to control group*

Nasometry outcomes for group A and B were compared with the mean nasalance score of the control group C, which was 15.83. For patients in group A, the mean nasalance scores were higher than subjects in group C and this difference reached statistical significance ( $p=0.001$ , 95% CI [2.05...7.52]) (Table 4a). There was virtually no difference in the mean nasalance scores for patients in group B and subjects in group C ( $p=0.088$ , 95% CI [-0.14...2.02]) (Table 4b).

### *Relation between nasometry and perceptual outcomes.*

In addition to the speech intelligibility between one and two-stage palatoplasty, we compared nasometry to perceptual analysis outcomes. The relation between the two outcomes is clear. Table 5 shows that for all parameters, nasometry scores increase when perceptual analysis of hypernasality increases ( $p<0.001$ ).

## **Discussion**

Numerous techniques have been described for the repair of cleft palate. All of these techniques aim to completely close the palate, avoid fistulas, provide a competent velum for normal speech, and allow harmonious facial growth<sup>27,10</sup>. The aim of this randomised controlled trial was to assess the effect of one-stage versus two-stage palatoplasty on speech and fistula formation. In a recently published systematic review<sup>10</sup> it was shown that all previous studies on the effect of one-stage or two-stage palatoplasty on speech<sup>28-34</sup> and fistula rates<sup>28-32</sup>, had a retrospective design.

Of the several surgical techniques available, we chose the levator myoplasty to repair the soft palate and the Bardach two flap technique to repair the hard palate<sup>21</sup>. This surgical technique was chosen because the surgeon who performed the surgery in all patients was very experienced in their use. We used the same technique in all patients. The only variation in procedure was the timing of surgery. The use of the same surgical procedures was done to

ensure that the study produced results for the timing of the surgery and not the technique used. This also ensured that we did not compromise on patient safety.

With regard to fistula rates four of the five studies<sup>29-32</sup> that were reviewed showed more fistula formation after two-stage palatoplasty as compared to one-stage palatoplasty. The findings of our study showed that there was no significant difference between one and two-stage palatoplasty with regard to fistula formation. This study has a low number of fistula formation. All the surgeries were performed by an experienced surgeon which could have reduced the number of patients having fistulas. Since

Of the eight studies that we reviewed regarding speech outcomes following one and two-stage palatoplasty, six studied speech patterns when the patients were adults<sup>28-32</sup> while two of the studies evaluated children<sup>33,34</sup>. Except for two studies,<sup>30,33</sup> all the other studies found that speech in various parameters was better in one-stage palatoplasty than in the two-stage palatoplasty.

In our study, there was no significant difference between groups A and B in the perceptual assessment. There were, however, slight differences in the means of the nasometry scores, which were 20.61 (SD 9.23), 16.77 (SD 2.15), and 15.83 (SD 1.76) for groups A, B, and C respectively. The difference between groups A and B reached statistical significance. However, it should be noted that a 4 point difference between groups A and B and a 5 point difference between groups A and C may not be clinically relevant. In the original normative study for these same passages in the SNAP Test-R<sup>6</sup> using a cohort of 231 normal speaking children in the United States, the mean was found to be 11. A score of 22 was suggested as a threshold value, where scores over that value would be considered abnormal. Therefore, the mean score for group A would still be considered within the normal range and the speech would unlikely be perceived as hypernasal, which is consistent with our results in the perceptual assessment.

We tested the speech of our experimental groups at the age of six years. The time of testing was prior to the maxillofacial growth spurt in young children<sup>35</sup>. Further study of speech should be done to determine if the length of the palate or the effectiveness of the velopharyngeal valve changes with further maxillofacial growth. Therefore, speech studies after the pubertal growth spurt should be done to evaluate changes in resonance. In addition, it will be important to study the effect of the two techniques on the growth of the midface and whether the growth has a role to play in the development of speech in such patients. Therefore, we intend to study the patients included in this trial for growth and again for speech after growth has been completed to evaluate changes in speech patterns.

#### *Limitations*

One limitation of this study is that we used only hypernasality as our speech outcome. We did not measure the ratings of audible nasal emission. Furthermore the perceptual rating of speech was performed by two speech pathologists. We did not perform a perceptual rating of hypernasality by untrained listeners. Brunnegard 2009<sup>36</sup> has shown that there is no significant difference in scoring of hypernasality between trained and untrained listeners. However, the same study showed that there was a significant difference for audible nasal emission which was scored higher by speech pathologists when compared to untrained listeners. In future studies we will elicit the response of untrained listeners when rating audible nasal emission.

In addition, we did not do a power analysis to determine the number of patients to be included in each group. This was because there were no previous trials that could be referred to. We decided to include 100 patients, which we felt would provide adequate power for the study to determine differences regarding speech. The results of the study showed that the power for fistula formation was probably low. The power of the study was adequate for studying hypernasality based on the positive trends seen in all measurements.

## **Conclusion**

This randomized controlled trial concludes that there is no difference in fistula rates between one and two-stage palatoplasty. There was also no difference in ratings of hypernasality between the two groups. Although the mean nasalance of the one-stage group was a little higher than the two-stage group and the difference was statistically significant, the difference may not be clinically relevant as the score was still in the borderline/normal range.

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## **FIGURE LEGENDS**

**Figure 1a. Pre-operative view of the soft palate**

**Figure 1b. Dissection of the oral mucosa above the muscles of the soft palate**

**Figure 1c Levator myoplasty, while ensuring no dissection of the tensor veli palatine muscle**

**Figure 1d Post-operative view of the soft palate**

**Figure 2. Flow diagram of the workflow through the trial**

## **TABLE LEGENDS**

**Table 1. Reliability of test-retest analysis of nasalance scores. (Nasalance scores represent the ratio of nasal acoustic energy divided by the total acoustic energy [nasal + oral] and converted to a percentage score between 0 and 100.) Units for DME and difference are the same as the variables tested.**

**Table 2. Comparison of nasalance scores (standard deviation) between group A and B, using t-tests at 6 years of age. The table compares mean values of each.**

**Table 3. Comparison of perceptual analysis outcomes between group A and B, using Chi-Square tests. The table compares the number of patients who have had scores of 0 (normal) with scores of 1, 2 or 3 (Hypernasal).**

**Table 4a. Comparison of mean outcomes (standard deviation) of nasometry between experimental groups A (n=50) and control group C (n=20) using t-tests.**

**Table 4b. Comparison of mean outcomes (standard deviation) of nasometry between experimental groups B (n=50) and control group C (n=20) using t-tests.**

**Table 5. Relation between mean nasometry outcomes (standard deviation) and perceptual analysis outcomes (n=number of patients) for each parameter. All p-values refer to ANOVA.**

Table 1. Reliability of test-retest analysis of nasalance scores. (Nasalance scores represent the ratio of nasal acoustic energy divided by the total acoustic energy [nasal + oral] and converted to a percentage score between 0 and 100.) Units for DME and difference are the same as the variables tested.

	<b>Reliability Coefficient</b>	<b>DME</b>	<b>Difference</b>	<b>P value</b>	<b>95% CI</b>
Bilabial Plosives	0.895	2.06	1.03	<0.001	[0.45...1.61]
Lingual Alveolar Plosives	0.927	2.14	1.84	<0.001	[1.24...2.44]
Velar Plosives	0.910	2.22	1.55	<0.001	[0.93...2.17]
Sibilant Fricatives	0.912	2.38	1.11	0.001	[0.44...1.78]
Sibilant Fricatives WO Nasals	0.940	2.03	0.37	0.201	[-0.20...0.94]

Table 2. Comparison of nasalance scores (standard deviation) between group A and B, using t-tests at 6 years of age. The table compares mean values of each.

	<b>Group A</b>	<b>Group B</b>	<b>Difference</b>	<b>P value</b>	<b>95% CI</b>
Bilabial Plosives	19.98 (8.05)	17.13 (2.80)	2.85	0.021	[0.44...5.26]
Lingual Alveolar Plosives	20.42 (10.32)	16.42 (2.63)	4.00	0.010	[0.98...7.02]
Velar Plosives	20.57 (9.48)	17.12 (2.85)	3.45	0.017	[0.65...6.25]
Sibilant Fricatives	21.21 (10.42)	17.38 (2.94)	3.83	0.015	[0.76...6.90]
Sibilant Fricatives without Nasals	20.89 (10.70)	15.80 (2.52)	5.09	0.002	[1.97...8.21]
<b>Mean of nasalance scores</b>	<b>20.61 (9.23)</b>	<b>16.77 (2.15)</b>	<b>3.84</b>	<b>0.006</b>	<b>[1.16...6.53]</b>

Table 3. Comparison of perceptual analysis outcomes between group A and B, using Chi-Square tests. The table compares the number of patients who have had scores of 0 (normal) with scores of 1, 2 or 3 (Hypernasal).

Score	Single Words		Sentences	
	A	B	A	B
0	32	30	35	35
1, 2 or 3	18	20	15	15
Fisher's Exact P: 0.837		Fisher's Exact P: 1.000		

Legend. Scores: 0: normal, 1: mild hypernasality, 2: moderate hypernasality, 3: severe hypernasality.

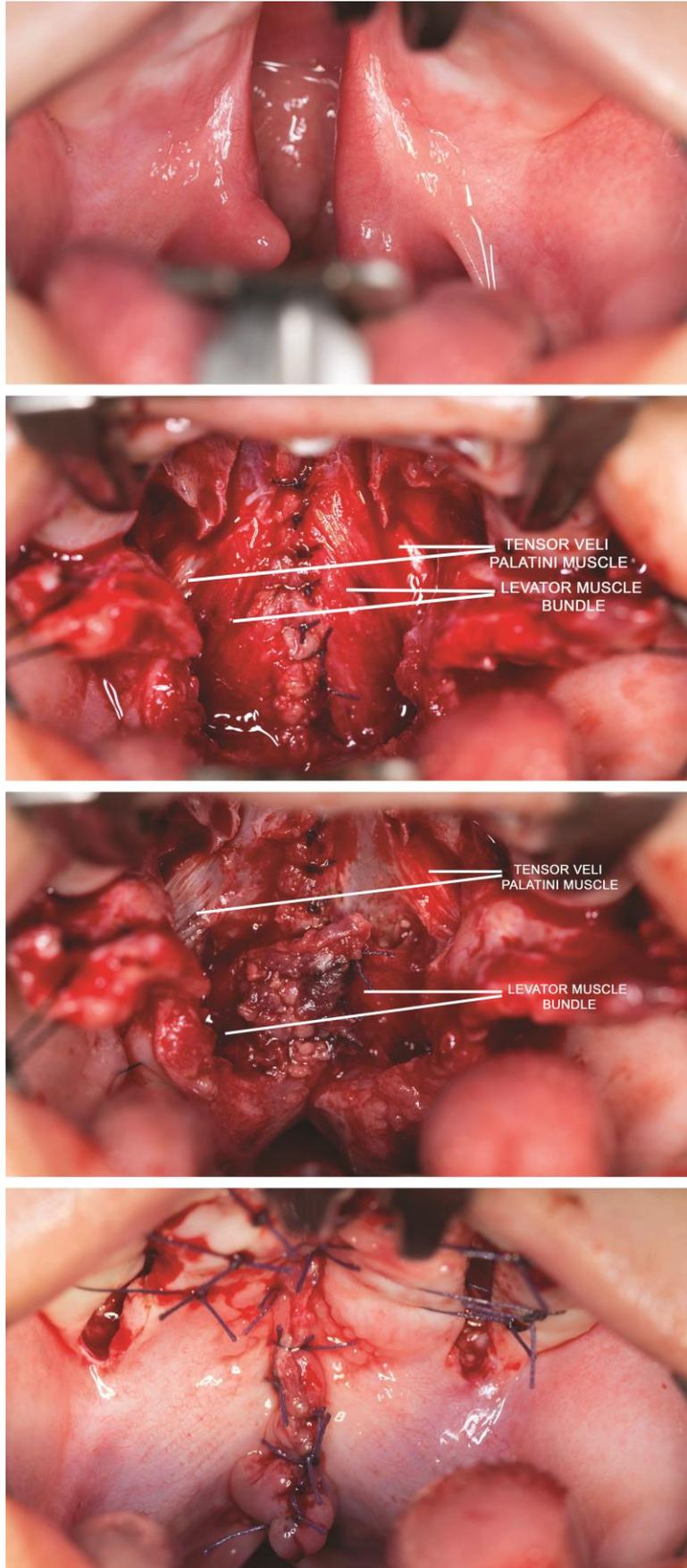
Table 4a. Comparison of mean outcomes (standard deviation) of nasometry between experimental groups A (n=50) and control group C (n=20) using t-tests.

	<b>Group A</b>	<b>Group C</b>	<b>Difference</b>	<b>P value</b>	<b>95% CI</b>
Bilabial Plosives	19.98 (8.05)	14.80 (2.28)	5.18	<0.001	[2.69...7.67]
Lingual Alveolar Plosives	20.42 (10.33)	16.08 (2.6)	4.35	0.008	[1.20...7.49]
Velar Plosives	20.57 (9.48)	15.68 (3.53)	4.90	0.028	[0.53...9.26]
Sibilant Fricatives	21.21 (10.42)	16.50 (3.22)	4.71	0.052	[-0.04...9.46]
Sibilant Fricatives WO Nasals	20.89 (10.70)	16.10 (4.49)	4.79	0.058	[-0.17...9.75]
<b>Mean of nasalance scores</b>	<b>20.61 (9.23)</b>	<b>15.83 (1.76)</b>	<b>4.78</b>	<b>0.001</b>	<b>[2.05...7.52]</b>

Table 4b. Comparison of mean outcomes (standard deviation) of nasometry between experimental groups B (n=50) and control group C (n=20) using t-tests.

	<b>Group B</b>	<b>Group C</b>	<b>Difference</b>	<b>P value</b>	<b>95% CI</b>
Bilabial Plosives	17.13 (2.8)	14.80 (2.28)	2.33	0.001	[0.92...3.74]
Lingual Alveolar Plosives	16.42 (2.63)	16.08 (2.6)	0.35	0.621	[-1.04...1.73]
Velar Plosives	17.12 (2.85)	15.68 (3.53)	1.45	0.078	[-0.17...3.06]
Sibilant Fricatives	17.38 (2.94)	16.50 (3.22)	0.88	0.275	[-0.72...2.48]
Sibilant Fricatives WO Nasals	15.80 (2.52)	16.10 (4.49)	-0.30	0.781	[-2.50...1.90]
<b>Mean of nasalance scores</b>	<b>16.77 (2.16)</b>	<b>15.83 (1.76)</b>	<b>0.94</b>	<b>0.088</b>	<b>[-0.14...2.02]</b>

**Figure 1**



**Figure 2**

**Flow diagram of the workflow through the trial**

