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Abstract

Objectives:

Patients with mandibular insufficiency can be predisposed to obstructive sleep apnea (OSA). The objective of this study was to systematically review the international literature for mandibular advancement surgeries (MAS) as treatment for adult OSA, and then to perform a meta-analysis.

Methods:

Four authors searched five databases from the inception of each database through April 5, 2017. The PRISMA statement was followed.

Results:

972 studies were screened, 84 were downloaded, and 11 (57 patients) met criteria. In patients with mandibular insufficiency, MAS reduced apnea-hypopnea index (AHI) (50 patients) from 45.9±24.7 to 6.2±10.4 events/hr (87% decrease). The lowest oxygen saturation (LSAT) (55 patients) increased from 71.9±14.6% to 89.0±11.0% The AHI mean difference was -34.8 events/hr [95% CI -43.9, -25.8]. The AHI standardized mean difference was -1.8 [95% CI -2.5, -1.2] (indicating a large magnitude of effect). Surgical cure was seen in 75% of those with >16mm of mandibular advancement vs. 35% of those with <16mm of advancement [Odds Ratio 5.5; 95% CI 1.06-28.4; Chi Square p = 0.035].

Conclusions:

The current literature supports isolated mandibular advancement as an efficacious treatment modality for adult OSA in select patients with mandibular insufficiency.

Keywords: Mandibular Advancement; Sleep Apnea Syndromes; Systematic Review; Meta-Analysis

Introduction

Obstructive Sleep Apnea (OSA) remains an ongoing concern for the medical and surgical communities due to its effects on sleep quality, and its associations with increased cardiovascular mortality (Somers et al. 2008). Of the many causes of OSA, the small or retrognathic mandible is an anatomical predisposition that is well documented to contribute to OSA severity. One of the leading treatments that has emerged for retrognathia is mandibular distraction osteogenesis (MDO), a surgical procedure that induces histogenesis by progressively advancing divided segments of the mandibular body (Natu et al. 2014). Additionally, mandibular advancement (MA) with placement of plates and screws has been used as well. Collectively, we will refer to MDO and MA as mandibular advancement surgeries (MAS).

The use of MAS for the treatment of OSA in congenital retrognathia has become increasingly common, and previous systematic reviews have been performed that address its success in children (Breik et al. 2016, Tsui et al. 2016). However, published results are relatively sparse for the procedure's benefit in acquired retrognathia of adulthood, and a meta-analysis of those published results has yet to be done to quantify the procedure's benefit.

The objective of this study was to systematically review all international publications reporting polysomnography data for MAS as an isolated treatment for OSA in adult patients, and then perform a meta-analysis with the available data. The study inclusion criteria were as follows using the PICOS acronym: (1) ***Patients:*** any adult patient (≥18 years old) with obstructive sleep apnea; (2) ***Intervention:*** mandibular distraction osteogenesis or mandibular advancement surgeries; (3) ***Comparison:***

polysomnography data pre-surgical and post-surgical; (4) ***Outcomes:*** oxygen desaturation index (ODI), apnea-hyponea index (AHI), respiratory disturbance index (RDI), Lowest oxygen saturation (LSAT), mean oxygen saturation (MSAT), sleepiness, quality of life; (5) ***Study design:*** any study design from case reports through randomized controlled-trials.

Methods

Protocol

The Tripler Army Medical Center approved this study via the protocol TAMC 16N14 (systematic review and meta-analysis).

Study eligibility criteria

Studies were included without any limitations based on language or the year of publication. Articles were excluded if, in addition to MAS, surgical procedures known to affect obstructive sleep apnea (e.g. maxillary advancement, genioplasty, palate surgery etc) were also performed. Concomitant TMJ arthroplasty was not considered a reason for exclusion.

Information Sources

The databases that were searched included Google Scholar, The Cochrane Library, Embase, Cumulative Index to Nursing and Allied Health (CINAHL) and PubMed/MEDLINE. The searches were initiated in October 15, 2015 and were completed April 5, 2017. The databases were each individually searched from the initiation of each database.

Search Strategy

An example of a search strategy, which we used in PubMed/MEDLINE as follows: surgery AND (“mandibular distraction” OR “distraction osteogenesis" OR "mandibular advancement”) AND (“hypersomnia sleep apnea syndrome” OR OSA OR “sleep apnea” OR “sleep apnoea”).

<u>Study Selection and Data Collection</u>

Four authors (M.C., J.A., S.M. and M.N.) independently searched the international literature for relevant studies to include in this review. Titles and abstracts were reviewed first, and the studies that were potentially relevant were each downloaded in full text form. Once the manuscripts were downloaded, they were independently reviewed by at least two co-authors for inclusion. Data was extracted from the manuscripts and documented in a table. If a study did not report all the data necessary for inclusion in the meta-analysis, or if there was an unresolvable discrepancy in the data, then the authors were contacted at least twice based on the contact information from the manuscript.

<u>Data Items</u>

If a study provided both AHI and obstructive apnea-hypopnea index (OAHI), OAHI was used preferentially as we are evaluating the effect of surgery on obstructive sleep apnea and not central sleep apnea. If multiple follow-up polysomnography measurements were provided by a study, then the data from the most recent polysomnogram was used (so long as no additional surgeries were performed).

<u>Summary measures:</u>

Summary measures included the weighted mean differences (MD) and the standardized mean differences (SMD). The associated 95% confidence intervals [95%

CI] were also calculated based on the data. The magnitudes of effect for SMD were assigned using Cohen's guidelines as small = 0.2, medium = 0.5, and large = 0.8 (Cohen 1988).

Heterogeneity and Risk of Bias

For the meta-analysis, Review Manager Software (REVMAN) version 5.3 (Copenhagen: The Nordic Cochrane Centre: The Cochrane Collaboration, 2014) was used for data analysis. REVMAN was used to calculate the Cochrane Q statistic (Q statistic), and based on previously published studies a value ≤0.10 was deemed statistically significant (Lau et al. 1997). Another measure of heterogeneity (inconsistency) was calculated by REVMAN as well (I^2 statistic), and values were defined as follows: 25% (low), 50% (moderate) and 75% (high) levels of inconsistency (Higgins et al. 2003).

Sensitivity analysis

After performing the meta-analysis and calculating the Q statistic and I^2 statistic, if there was heterogeneity, then a sensitivity analysis was performed in order to identify which study or studies were responsible.

Results

The search strategy yielded 972 studies, of which 84 were potentially relevant and were downloaded in their full versions. Studies were excluded for absent pre- and post-surgical polysomnography, for inadequate separation of results from pediatric patients, or for the inclusion of additional surgeries besides MDO. In total, 11 articles met inclusion and exclusion criteria (Paoli et al. 2001, Li et al. 2002, Harada et al. 2003, Wang et al. 2003, Woodson et al. 2003, Zhou et al. 2005, Hamada et al. 2007, Liang et al. 2007, Feiyun et al. 2010, Manikandhan et al. 2014, Yadav et al. 2014). Figure 1 demonstrates the exclusions at each stage.

Included studies were evaluated using The National Institute for Health and Clinical Excellence (NICE) quality assessment tool (Methods for Development of NICE Public Health Guidance. London). The results can be seen in Table 1.

Meta-analysis of the eleven studies included demonstrated a reduced AHI (50 patients) from a Mean ± SD of 45.89±23.73 to 6.15±10.44 events per hour (86.60% decrease). The LSAT (55 patients) increased from a mean ± SD of 71.93±14.63 to 88.95±10.95 (See Table II).

A subanalysis using random effects modeling was performed on the four studies with AHI/RDI data in which it could be combined (29 patients), and there was an AHI/RDI mean difference (MD) of -34.80 events per hour [95% CI -43.86, -25.75], overall effect (Z) = 7.53, P value <0.00001, Q statistic P value = 0.54 (no heterogeneity present), I^2 = 0% (no inconsistency). The AHI standardized mean difference (SMD) was -1.83 [95% CI -2.48, -1.17] (large magnitude of effect), overall effect Z = 5.49, P value < 0.00001, Q statistic P value 0.97 (no heterogeneity present), I^2 = 0% (no inconsistency) (See Figure 2).

Random effects subanalysis of the five studies with LSAT data (36 patients) demonstrated an LSAT mean difference (MD) of 12.80% [95% CI 4.86, 20.73], overall effect Z = 3.16, P value = 0.002, Q statistic P value = 0.01 (heterogeneity present), I^2 = 70% (inconsistency present). After removing the study by *Li et al.* 2002 in a Sensitivity Analysis, MD contained no heterogeneity (Q statistic P value = 0.76) and no inconsistency ($I^2 = 0\%$). The LSAT SMD was 1.15 [95% CI 0.63, 1.67] (large magnitude of effect), overall effect Z = 4.35, P value < 0.0001, Q statistic P value 0.77 (no heterogeneity present), $I^2 = 0\%$ (no inconsistency) (See Figure 3).

Among the individual patient data available, patient differences between pre- and post-operative mandibular advancement are summarized in Table 3. There were significantly decreased AHI, RDI and LSAT on PSG in MAS post-operative patients (p < 0.001). Over half of patients receiving mandibular advancement were cured of their disease by AHI criteria (AHI <5 events per hour), and 80% were cured by RDI criteria (RDI <5 events per hour). Surgery was successful in nearly all patients (defined as 50% reduction in AHI/RDI and a postoperative AHI/RDI<20). Additionally~~, among the individual patient data, there were,~~ on regression analysis, significantly increased odds of surgical cure were found among patients with >16mm of mandibular advancement vs. <16mm of advancement [Odds Ratio 5.5; 95% CI 1.06-28.4; Chi Square p = 0.035] (See Figure 4). The 16 mm cutoff demonstrates that surgical cure was seen in 75% of those with >16mm of mandibular advancement vs. 35% of those with <16mm of advancement

Discussion

The major finding from this study is that OSA has been shown to improve significantly after mandibular advancement or mandibular distraction osteogenesis in adult patients with mandibular insufficiency. This significant improvement is demonstrated by the dramatic reduction in the apnea-hypopnea index from 46 to 6 events per hour (87% decrease) and also the dramatic increase in the lowest oxygen saturation from 72% to 89%. To our knowledge, this meta-analysis is the first to systematically review the literature and provide a summary. Given that there was no heterogeneity (Q-statistic) and no inconsistency (I^2), the currently published studies are consistent in their findings of improved OSA outcomes.

Although there is no previous meta-analysis on the topic that we could find, there have been other skeletal surgery meta-analyses for adult OSA, such as that for genioplasty/genioglossus advancement, maxillary expansion/maxillomandibular expansion and maxillomandibular advancement (Abdullatif et al. 2016, Zaghi et al. 2016, Song et al. 2017). Based on improvement in apnea-hypopnea index, previously the most successful of skeletal surgeries for adult OSA was maxillomandibular advancement (MMA), and prior reviews have documented that AHI reduced from 57.2 to 9.5 events/hr (83% reduction) (Zaghi et al. 2016). The finding of an 87% reduction in the apnea-hypopnea index for a mandibular advancement alone was quite surprising given that an MMA, which involves moving the maxilla as well, had an 83% reduction. However, these are different population groups, as many patients who undergo MMA don't necessarily have significant micrognathia or retrognathia. Rather an MMA gains a great deal of its benefit from maxillary advancement, counter-clockwise rotation, and resultant lateral pharyngeal wall stability (Liu et al. 2016). In some patients undergoing MMA surgery as treatment for OSA, the maxillomandibular complex is moved as an entire unit, keeping the occlusion the same. However, in patients with micrognathia or retrognathia, and the only surgery is mandibular advancement – therefore, by definition, because only the mandible is moving forward – the dental occlusion will change.

The findings of this meta-analysis are logical, given that a small mandible or retrodisplaced mandible will cause the tongue to be posteriorly displaced, and therefore will be crowding the upper airway. Therefore, moving the mandible anteriorly will move the tongue anteriorly, which will also open the upper airway. It has been shown that tongue-lip adhesion and mandibular advancement surgeries have improved obstructive sleep apnea in children as demonstrated by two studies evaluating surgery in children with Pierre-Robin sequence (Tsui et al. 2016, Camacho et al. 2017). Although no previous meta-analysis on adults has been performed, there have been eleven studies in the international literature confirming that mandibular advancement alone can improve OSA.

There are limitations to this study. The current literature is limited to case reports and small case series. However, it would be difficult to perform randomized trials for patients with significant mandibular insufficiency given that the advancement of the mandible is a targeted and patient-specific surgery which has been demonstrated to improve function, occlusion, and OSA outcomes. Given that the medical and surgical literature can be biased against negative findings, it is possible that studies demonstrating a worsening of OSA or no difference in OSA may have either not been submitted for publication or were rejected from publication.

Conclusions

The current international literature has demonstrated a significant improvement in adult obstructive sleep apnea after isolated mandibular advancement or mandibular distraction osteogenesis in patients with mandibular insufficiency.

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Year, Study Authors, Design	Study Site	Outcomes Analyzed	Evidence level	1	2	3	4	5	6	7	8
2014 Yadav, PCS	India	AHI. LSAT	V	No	Yes	No	Yes	Yes	No	Yes	Yes
2014, Manikandhan, PCS	India	AHI. LSAT	V	No	Yes	Yes	No	Yes	No	Yes	Yes
2010, Feiyun, PCS	China	RDI. LSAT	III	No	Yes	No	No	Yes	No	Yes	No
2007, Hamada, RCR	Japan	AHI. LSAT	NA	NA	NA	NA	NA	NA	NA	NA	NA
2007, Liang, RCS	China	LSAT	IV	No	Yes	Yes	Yes	No	No	Yes	No
2005, Zhou, RCS	China	AHI. LSAT	IV	No	Yes	Yes	Yes	No	No	Yes	No
2003, Wang, RCR	China	AHI LSAT	NA	NA	NA	NA	NA	NA	NA	NA	NA
2003, Woodson, RCR	USA	RDI	NA	NA	NA	NA	NA	NA	NA	NA	NA
2003, Harada, RCR	Japan	AI. LSAT	NA	NA	NA	NA	NA	NA	NA	NA	NA
2002, Li, PCS	USA	RDI. LSAT	V	No	Yes	Yes	No	Yes	Yes	Yes	No
2001, Paoli, RCR	France	AHI. LSAT	NA	NA	NA	NA	NA	NA	NA	NA	NA

Table 1: General characteristics and quality criteria of included studies.
AHI = Apnea/Hypopnea Index; RDI = Respiratory Disturbance Index; AI = Apnea Index; LSAT = Lowest Oxygen Saturation.
NA = Not Applicable; PCS = Prospective Case Series; RCR = Retrospective Case Report.
*Quality Assessment of cases series studies checklist from National Institute for Health and Clinical Excellence (NICE): 1) Case series collected in more than one center, i.e. multi-center study? 2) Is the hypothesis/aim/objective of the study clearly described? 3) Are the inclusion and exclusion criteria (case definition) clearly reported? 4) Is there a clear definition of the outcomes reported? 5) Were data collected prospectively? 6) Is there an explicit statement that patients were recruited consecutively? 7) Are the main findings of the study clearly described? 8) Are outcomes stratified? (e.g., by abnormal results, disease stage, patient characteristics)?

Study Authors Year	N	Age	Pre-Op AHI/RDI	Post-Op AHI/RDI	AHI/RDI percent Change	Pre-Op LSAT	Post-Op LSAT
Yadav 2014	8	25.5±8.8	38.13±22.12	5.36±6.23	-85.94%	67.84±18.75	86.69±7.96
Manikandhan 2014	13	23.3±6.3	44.86±22.31	12.88±13.75	-71.29%	68.38±14.71	80.98±12.88
Feiyun 2010	16	27 (18-43)	47.3*	2.1*	-95.56%	75.4	98.2
Hamada 2007	1	31.3	41.4	4.8	-88.41%	77	87
Liang 2007	7	35±13.2	NR	NR	-	74.14±9.48	89.43±6.48
Zhou 2005	4	24.5±7.33	61.43±33.28	3.3±1.5	-94.63%	62.75±16.62	85.5±4.51
Wang 2003	1	36	96.2	5.8	-93.97%	NR	NR
Woodson 2003	1	48	38*	2^{*x}	-94.74%	NR	NR
Harada 2003	1	31	29.9^{+}	5.8^{+}	$-80.60\%^{+}$	77	87
Li 2002	4	54.5±10.1	39.73±20.33*	4.9±4.87*	-87.67%	84.5±3.32	87.5±3.32
Paoli 2001	1	44	23.4	11.9	-49.15%	56	83
Total	57	29.7±12.8	45.89±23.73	6.15±10.44	-86.60%	71.93±14.63	88.95±10.95

Table 2: Polysomnographic Data Pre- and Post-Mandibular Advancement Surgery. AHI=Apnea/hypopnea Index; RDI=Respiratory Disturbance Index; LSAT=Lowest oxygen saturation. N = Number; NR=Not Reported.

*=RDI; $^{+}$=Apnea Index; ^{x}=PSG performed with CPAP in place at 4cm H_2O

Characteristic	No. of Patients	Pre-MA	Post-MA	*P* Value
Age, mean (SD), y	57	30.2 (11.5)	NA	NA
Male, %	32/44	72.7	NA	NA
Preop BMI, mean (SD)	11	20.1 (5.9)	NA	NA
Polysomnography				
AHI, mean (SD), events/h	29	45.7 (25.0)	8.7 (10.4)	p < 0.001
AHI > 30 events/h, %	20/29	69.0	6.9	p < 0.001
AHI > 20 events/h, %	27/29	93.1	6.9	p < 0.001
RDI, mean (SD), des/h	5	39.4 (17.6)	4.9 (4.9)	p < 0.001
LSAT, mean (SD)	40	70.1 (14.6)	85.2 (9.0)	p < 0.001
Mandibular Advancement, mean (SD), mm	57	NA	16.1 (6.3)	NA
Surgical Cure, %				
AHI surgical cure	15/29	NA	51.7	NA
RDI surgical cure	4/5	NA	80	NA
Surgical Success, %				
AHI surgical success	26/29	NA	89.7	NA
RDI surgical success	5/5	NA	100	NA

Table 3: Individual differences between pre- and post-operative mandibular advancement patients. MA=Mandibular Advancement; BMI=Body Mass Index; AHI=Apnea/hypopnea Index; RDI=Respiratory Disturbance Index; LSAT=Lowest oxygen saturation; NA=Not Applicable.

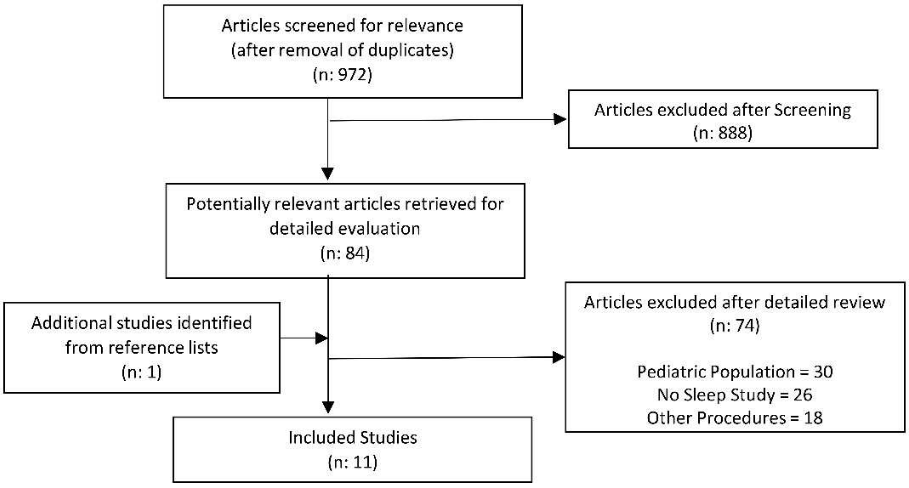
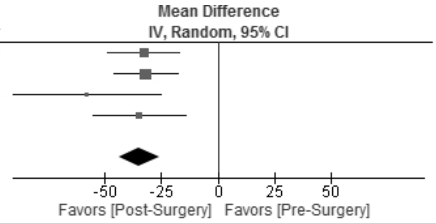


Figure 1: Flow diagram demonstrating literature search, study inclusion and exclusion.

	Post-Op			Pre-Op				Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Yadav 2013	5.36	6.23	8	38.13	22.12	8	32.3%	-32.77 [-48.69, -16.85]	2013
Manikandhan 2013	12.88	13.75	13	44.86	22.31	13	40.4%	-31.98 [-46.23, -17.73]	2013
Zhou 2005	3.3	1.5	4	61.43	33.28	4	7.7%	-58.13 [-90.78, -25.48]	2005
Li 2002	4.9	4.87	4	39.73	20.33	4	19.5%	-34.83 [-55.32, -14.34]	2002
Total (95% CI)			**29**			**29**	**100.0%**	**-34.80 [-43.86, -25.75]**	

Heterogeneity: Tau² = 0.00; Chi² = 2.17, df = 3 (P = 0.54); I² = 0%
Test for overall effect: Z = 7.53 (P < 0.00001)



	Post-Op			Pre-Op				Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Yadav 2013	5.36	6.23	8	38.13	22.12	8	27.7%	-1.91 [-3.15, -0.67]	2013
Manikandhan 2013	12.88	13.75	13	44.86	22.31	13	51.0%	-1.67 [-2.58, -0.76]	2013
Zhou 2005	3.3	1.5	4	61.43	33.28	4	10.4%	-2.15 [-4.17, -0.12]	2005
Li 2002	4.9	4.87	4	39.73	20.33	4	10.9%	-2.05 [-4.03, -0.07]	2002
Total (95% CI)			**29**			**29**	**100.0%**	**-1.83 [-2.48, -1.17]**	

Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 3 (P = 0.97); I² = 0%
Test for overall effect: Z = 5.49 (P < 0.00001)

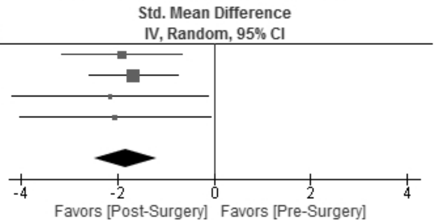
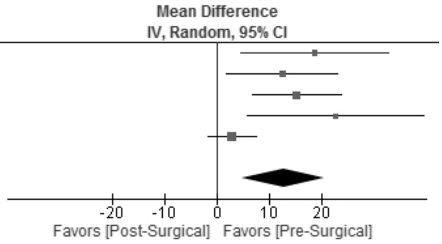


Figure 2: Mean Difference in AHI/RDI Pre- and Post-Mandibular Advancement Surgery, with 95% confidence Intervals (Top); Standardized Mean Difference in AHI/RDI pre- and post-Mandibular Advancement Surgery, with 95% confidence interval (Bottom).

Study or Subgroup	Post-Op Mean	Post-Op SD	Post-Op Total	Pre-Op Mean	Pre-Op SD	Pre-Op Total	Weight	Mean Difference IV, Random, 95% CI	Year
Yadav 2013	86.69	7.96	8	67.84	18.75	8	15.7%	18.85 [4.73, 32.97]	2013
Manikandhan 2013	80.98	12.88	13	68.38	14.71	13	20.0%	12.60 [1.97, 23.23]	2013
Liang 2007	89.43	6.48	7	74.14	9.48	7	23.0%	15.29 [6.78, 23.80]	2007
Zhou 2005	85.5	4.51	4	62.75	16.62	4	12.9%	22.75 [5.87, 39.63]	2005
Li 2002	87.5	3.32	4	84.5	3.32	4	28.3%	3.00 [-1.60, 7.60]	2002
Total (95% CI)			**36**			**36**	**100.0%**	**12.80 [4.86, 20.73]**	

Heterogeneity: Tau² = 52.40; Chi² = 13.27, df = 4 (P = 0.01); I² = 70%
Test for overall effect: Z = 3.16 (P = 0.002)



Study or Subgroup	Post-Op Mean	Post-Op SD	Post-Op Total	Pre-Op Mean	Pre-Op SD	Pre-Op Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Yadav 2013	86.69	7.96	8	67.84	18.75	8	22.4%	1.24 [0.14, 2.33]	2013
Manikandhan 2013	80.98	12.88	13	68.38	14.71	13	40.9%	0.88 [0.07, 1.69]	2013
Liang 2007	89.43	6.48	7	74.14	9.48	7	16.0%	1.76 [0.46, 3.06]	2007
Zhou 2005	85.5	4.51	4	62.75	16.62	4	8.5%	1.62 [-0.16, 3.40]	2005
Li 2002	87.5	3.32	4	84.5	3.32	4	12.2%	0.79 [-0.70, 2.27]	2002
Total (95% CI)			**36**			**36**	**100.0%**	**1.15 [0.63, 1.67]**	

Heterogeneity: Tau² = 0.00; Chi² = 1.80, df = 4 (P = 0.77); I² = 0%
Test for overall effect: Z = 4.35 (P < 0.0001)

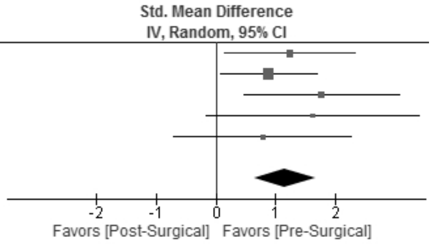


Figure 3: Mean Difference in LSAT Pre- and Post-Mandibular Advancement Surgery, with 95% confidence Intervals (Top); Standardized Mean Difference in LSAT pre- and post-Mandibular Advancement Surgery, with 95% confidence interval (Bottom).

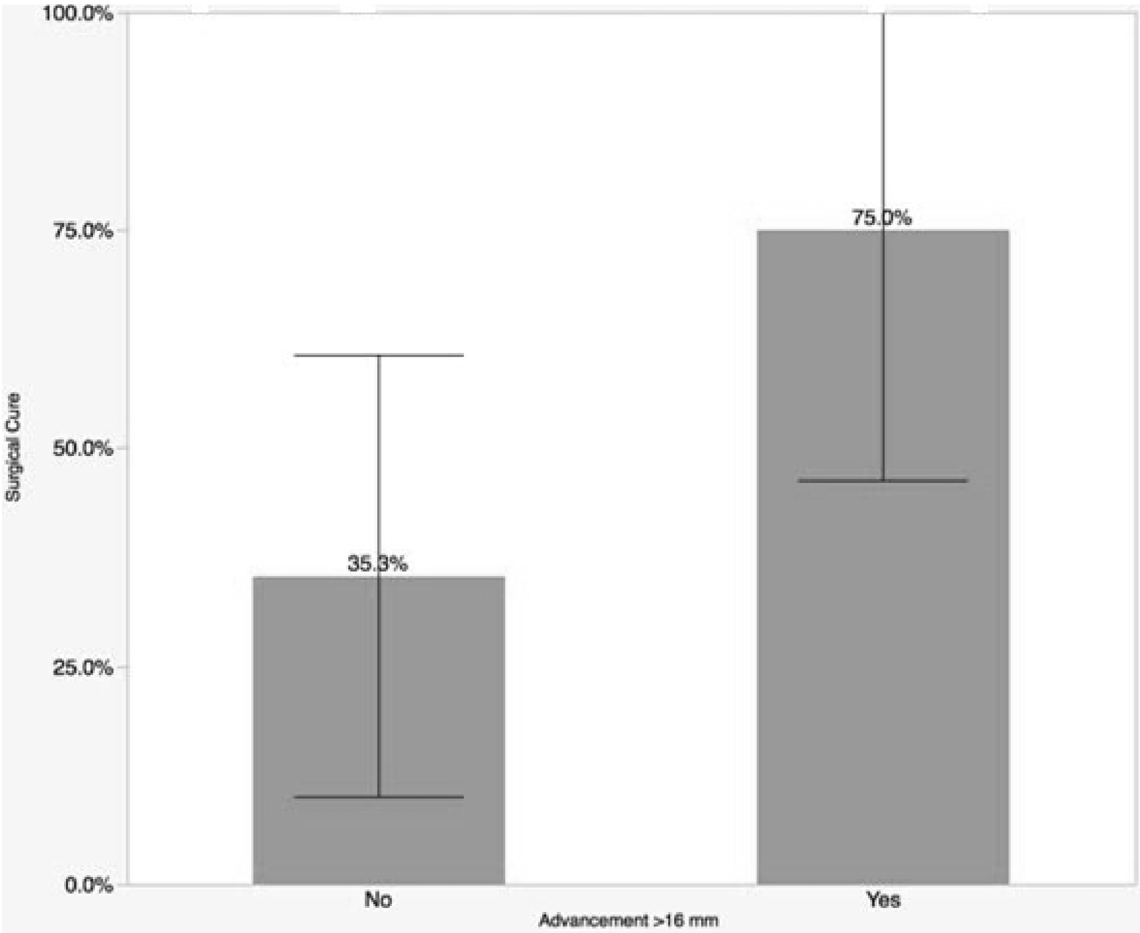


Figure 4: Surgical Cure by Mandibular Advancement >16mm (Yes/No). Surgical Cure set as an AHI<5 events per hour.