



Nonclosure Versus Closure of Buccal Mucosal Graft Harvest Site: A Systematic Review and Meta-Analysis of Patient-Reported Outcomes

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OBJECTIVE	To compare the postprocedural oral pain scale and other patient reported oral morbidities for non-closure vs closure of buccal mucosal graft (BMG) harvest sites through systematic review and meta-analysis of comparative studies.
METHODS	A systematic literature search was performed in September 2018. Nonrandomized comparative studies were summarized and randomized controlled trials were evaluated according to the Cochrane Collaboration recommendations. The outcomes assessed were: pain, perioral numbness, mouth opening tightness, and impairment of oral intake. Standardized mean difference, and relative risk with corresponding 95% confidence intervals were extrapolated. Effect estimates were pooled using the inverse variance method with a random-effects model. Subgroup analysis was performed according to the shape of the BMG harvested. PROSPERO registry (CRD42016043502).
RESULTS	A total of 269 patients from 4 randomized controlled trials were included for meta-analysis. Overall pooled effect estimates on the reported pain score assessed on postprocedural day 1, day 3-7 and 6 months, have shown no significant difference between the closure and nonclosure treatment groups. Subgroup analysis showed that rectangular shaped BMG harvest sites that were not closed had lower pain scores (standardized mean difference -0.90 , 95% confidence interval -1.70 , -0.10) on postoperative day 1. No reported short or long-term oral morbidities required further surgical intervention in either treatment group.
CONCLUSION	The evidence suggests that at 6-month follow-up, there is no overall significant difference between nonclosure and closure of BMG harvest sites. However, among rectangular shaped BMG, not closing the harvest site may lead to less immediate postoperative pain when compared to closure of the harvest site. UROLOGY 125: 213–221, 2019. © 2018 Elsevier Inc.

The buccal mucosal graft (BMG) for urethroplasty has gained popularity in the past few decades as the preferred autologous substitution tissue for complex hypospadias and urethral stricture disease.^{1,2} BMG is favored due to its availability, concealed donor site, ease of harvest, and tissue handling. Furthermore, current literature has illustrated good long-term surgical outcomes for BMG substitution augmented urethroplasty

for anterior urethral strictures and complex hypospadias repairs.^{3,4}

Traditionally, the management of the BMG harvest site has been to oppose the edges with sutures for primary healing and additional means for hemostasis.^{5,6} However, contemporary studies have determined that such approach may lead to oral morbidity, such as pain, effect on quality of life, and other long-term sequelae.^{2,6-8} An initial study presented as an abstract by Greenwell et al (2004), reported that the closure of the BMG harvest site may worsen the postprocedural oral pain and create problems of mouth opening with perioral numbness. They have recommended leaving the harvest site open to avoid these morbidities.⁹ Since then, there has been an ongoing debate whether or not closure of the site would render better postprocedural pain and lessen associated morbidity.¹⁰

Due to inconsistencies of the reported outcomes amongst published studies, surgical practices still vary. A

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recent survey has shown a diverse practice patterns of urologic reconstructive surgeons on the closure or not of BMG sites.¹¹ Hence, this systematic review and meta-analysis aims to evaluate available evidence on the effect of nonclosure vs closure of BMG harvest sites on postoperative oral pain and other patient-reported oral morbidities related to BMG harvest site management.

METHODOLOGY

The study protocol was registered in the PROSPERO registry (CRD42018106134) and performed according to the Cochrane Collaboration recommendations.¹² The reporting complies with the recommendations of PRISMA statement.¹³

Identification of the Literature

A medical librarian reference service specialist assisted on the systematic literature search performed on September 10, 2018 in the following electronic databases: Medline, Embase, Pubmed, Scopus, and the Cochrane Central Register of Controlled Trials. The reviewers also searched the ProQuest dissertations and theses global and clinicaltrial.gov site for possible unpublished studies. Additional inquiries were sent to investigators and authors regarding clarification and request for additional information on incomplete data. A sensitive search strategy was performed utilizing both medical subject headings and common terms; the detailed search string used for each electronic database is outlined in Appendix A. No language restriction was imposed on the literature search. An extensive and comprehensive search for eligible studies was carried out to minimize reporting bias, publication bias, and their potential impact. A manual search of international urology conference abstracts and cross-references of reviews on the topic that met our inclusion criteria were also performed for potentially relevant titles.

The primary outcome measure determined in this meta-analysis was the continuous scale of patient-reported oral pain score perceived on postoperative day-1, days 3-7, and 6 months. Other postprocedural patient-reported outcomes in continuous scale such as: perioral numbness, oral tightness, fluid intake, and solid intake discomfort were assessed as secondary outcomes. This meta-analysis also assessed secondary outcomes as dichotomous data: number of patients who reported resuming a regular diet on post-op days 3-7 and number of patients who reported perioral numbness and oral tightness for mouth opening on post-op days 3-7 and 6 months. When available the additional effect estimates pooled for other follow-up time intervals such as 3-4 weeks and 3-months, are provided as supplementary tables.

Evaluation of the literature

Two reviewers independently identified, screened and evaluated the citations and abstracts of scientific literature related to BMG harvesting site management in both adult and pediatric populations. This systematic review considered all comparative studies that assess patient-reported outcomes and morbidities related to nonclosure vs closure of BMG harvest sites. The articles that either reviewer flagged were retrieved for further full-text evaluation. Two physician reviewers then independently reviewed each full-text article and determined whether inclusion criteria were met. When a study had multiple publications, only the most recent complete data reported was considered for further data extraction. All reviewers were knowledgeable about the principles of critical appraisal and experienced in performing

systematic reviews. Any disagreement was resolved through consensus between reviewers, and further reviewed by a senior physician researcher to settle discrepancies.

The identified randomized controlled trials (RCTs) that compared nonclosure vs closure (as control) of BMG harvest site were appraised using the risk of bias tool according to the Cochrane Collaboration recommendations for intervention reviews.¹² Specifically, the randomization sequence generation; allocation concealment; blinding of participants, providers, and outcome assessors; completeness of outcome data; selective outcome reporting; and other potential sources of bias were assessed. A funnel-plot was generated to explore the possibility of publication bias.¹² The outcomes of the RCTs were then extracted and included for meta-analysis. The nonrandomized comparative studies (retrospective and prospective cohorts) were excluded for meta-analysis but summarized.

Data Extraction, Data Synthesis and Data Classification

Details on the study characteristics and primary outcome assessment were extracted and tabulated by 1 reviewer and counter verified by another. For both the meta-analysis and systematic review, details of the included study trials, such as study source, study population age, BMG harvest techniques (closure suture, intraoperative local anesthetics, and hemostasis approach), graft harvest site, shape, size and area, study outcome assessed, survey used, intervention group sample size, follow-up duration, pain meds, and data results or conclusion remarks were summarized in a table. The RevMan5 program, downloaded from www.cochrane.org, was used for data synthesis, analysis, forest plot, and funnel-plot construction.¹⁴ Furthermore, using the RevMan5 calculator,¹⁴ the patient-reported outcomes assessed such as pain score mean and standard deviation were derived and extrapolated for the treatment groups according to the published report of each included study or private communication with the authors. When incomplete data were encountered, and the study authors did not respond or insufficient data were provided, the effect estimates for each treatment group were derived from the published per protocol analysis or extrapolated using the reported mean difference and *P* value.

Measures of Treatment Effect

The standardized mean difference (SMD) with corresponding 95% confidence intervals (CIs) was generated for between-group treatment effect estimation. The SMD expresses the effect size of the intervention relative to the variability observed within each individual study; therefore, it is considered more generalizable and appropriate to standardize the results of different studies that assess the same outcome however measured on different validated scales.^{12,15} When the event rate of oral morbidity was described by the included study, they were extrapolated as dichotomous data and pooled as relative risk (RRs) with corresponding 95% CIs. To mitigate the methodological diversity, after standardization of effect estimates using the SMD or RR and corresponding 95% CI, data were pooled using the inverse variance method with a random-effects model to generate an average treatment effect.¹⁶

Assessment of Heterogeneity, Subgroup Analysis and Publication Bias

The χ^2 statistical test was used to assess the heterogeneity among included studies. Because only a small number of trials with small sample sizes were included; a *P* value of <0.10 was used in this

meta-analysis to confirm heterogeneity. Furthermore, the I^2 statistic was used to quantify the variations between the studies; if a value >40% was found, then significant heterogeneity was assumed.¹² A preplanned subgroup analysis was performed to verify the identified study variation. Subgroup analysis was performed if adequate numbers of studies were available for outcome data extraction. We intended to perform subgroup analysis according to study design, population difference (age/sex), and protocol differences (techniques or BMG shape harvest or local anesthesia infiltration). A funnel-plot was generated for visual illustration for exploration of publication bias likelihood.

RESULTS

A total of 797 titles were available of which, based on abstracts, 137 full-text articles were retrieved after initial screening for eligibility. One-hundred twenty-eight studies were excluded due to reasons enumerated in [Supplementary Figure 1](#), which also summarizes the literature search process. Nine studies were determined to be eligible for systematic review with 4 RCTs included for meta-analysis¹⁷⁻²⁰ ([Table 1](#)) and 5 nonrandomized comparative studies,²¹⁻²⁵ which are summarized in [Table 2](#). In brief, 4 of the 5 nonrandomized studies concluded no significant differences in oral morbidity assessment between the treatment groups.²²⁻²⁵ One study reported the mean daily pain score was consistently higher within the closure group, reaching statistical significance on postoperative days 4 and 5.²¹

Study Characteristics of RCTs

Four RCTs included were conducted in different countries¹⁷⁻²⁰ and designed as randomized nonblinded parallel controlled trials. The study population ages ranged from 17 to 72 years old; and no pediatric population studies were available. Across all studies, local anesthesia with adrenaline solution was used for hydrodistention prior to harvest and bipolar diathermy with wet gauze or cottonoid soaked in epinephrine were used for hemostasis. BMGs were harvested mainly from the inner cheek with one study also using the lower lip in some of their patients.¹⁷ Two studies harvested a rectangular shaped graft^{17,18}, while the other 2 harvested ovoid shaped grafts.^{19,20} Different closure techniques and sutures were used by the studies, most using continuous sutures.¹⁷⁻¹⁹ One study used a 5-point pain scale,¹⁷ while the other studies used 10 or 11-point pain scales for oral pain assessment.¹⁸⁻²⁰ A detailed description of the included RCT studies is summarized in [Table 1](#). According to the Cochrane risk of bias assessment, the included studies were considered to be of very low to moderate methodological quality with high risk of bias for performance and detection bias due to inability to blind the patients and surgeons. Two studies were further noted to have a high risk of attrition bias due to missing data.^{19,20} [Figure 1](#) summarizes the effect of intervention, and [Figure 2](#) summarizes the risk of bias assessment of the individual studies.

Effect of Intervention

Overall pooled effect estimates from the 4 eligible RCT studies (269 subjects: 139 nonclosure, and 130 closure), demonstrated no significant difference in oral pain perception associated with nonclosure or closure of the BMG harvest site for postprocedure day-1 (SMD -0.47; 95%CI -1.01, 0.07), day 3-7 (SMD 0.16; 95%CI -0.23, 0.54) and 6-month follow-up (SMD -0.04; 95%CI -0.28, 0.20; [Fig. 2A-C](#), respectively). However, significant moderate to considerable interstudy heterogeneity was

noted among the 4 studies at the postoperative day-1 and day 3-7 pain perception assessment ($\chi^2 = 12.32$, $P = 0.006$, $I^2 = 76%$, $\chi^2 = 6.64$, $P = 0.08$, $I^2 = 55%$; respectively). The source of heterogeneity was identified in the study by Muruganandam (2009), which could be due to its methodological difference, baseline group discrepancies and 5-point pain scale used to evaluate the outcome.¹⁷ When the study was removed with repeat sensitivity analysis, the heterogeneity was not significant ($\chi^2 = 3.05$, $P = 0.22$, $I^2 = 34%$, $\chi^2 = 4.00$, $P = 0.14$, $I^2 = 50%$, for day-1 and days 3-7; respectively). However, the overall pooled effect estimates for pain perception remained unchanged (SMD -0.25, 95%CI -0.60, 0.11, SMD 0.30 95%CI -0.12, 0.71; respectively).

The predetermined subgroup with sensitivity analysis was performed according to graft shape. For postoperative day-1, the rectangular graft harvest subgroup revealed significantly less pain perceived by the patients in the nonclosure group (SMD -0.90, 95%CI -1.70, -0.10). However, the ovoid graft harvest subgroup did not show any difference between groups (SMD -0.11, 95%CI -0.66, 0.44). [Supplementary Table 1](#) summarizes the pooled effect estimates at different time points, which showed no further differences in pain intensity perceptions.

Two studies^{19,20} reported on the discomfort or impairment of oral fluid and solid intake. The pooled effect estimates from these studies demonstrated significantly higher pain discomfort or impairment for fluid intake on post-op day-1 and days 3-7 within the nonclosure group (SMD 0.39, 95%CI 0.07, 0.72 and SMD 0.38, 95% CI 0.05, 0.72; respectively). However, solid intake discomfort was higher in the nonclosure group only on days 3-7 postprocedure (SMD 0.49, 95% CI 0.16, 0.82; [Supplementary Tables 2 and 3](#)).

The evaluation for mouth opening tightness and perioral numbness pooled from the 2 studies^{19,20} assessed using continuous scales showed significantly lower mouth opening impairment in the nonclosure group at day-1 postprocedure assessment (SMD -0.34, 95%CI -0.66, -0.01), and was noted to have no differences between groups beyond the follow-up time period ([Supplementary Table 4](#)). No significant differences on perioral numbness were reported between the 2 treatment groups across all the follow-up time periods evaluated ([Supplementary Table 5](#)).

The pooled effect estimates on dichotomous data for number of patients reporting perioral numbness and mouth opening tightness or impairment from the 3 studies, showed no significant difference between the groups. However, significant moderate inter-study heterogeneity was noted for both days 3-7 and 6-month time period assessments ($\chi^2 = 4.74$, $P = 0.09$, $I^2 = 58%$, $\chi^2 = 4.80$, $P = 0.09$, $I^2 = 58%$; respectively). Subgroup analysis was performed and showed that both subgroups pooled effect estimates from the studies that harvested rectangular shaped or ovoid shaped BMGs, have illustrated no significant differences between the groups for perioral numbness and mouth opening tightness on days 3-7 postprocedure and 6-month follow-up ([Supplementary Tables 6 and 7](#)). Likewise, with the pooled estimates from 2 studies that assessed return of regular diet at postprocedural days 3-7 showed no difference between groups (RR 1.19, 95% CI 0.98, 1.44).

Lastly, all studies have reported that neither treatment group had postoperative bleeding or long-term complications requiring further surgical interventions ([Tables 1 and 2](#)). Although only a few studies were included, based on the funnel-plot ([Supplementary Figure 2](#)) generated from the standard error of SMD from all

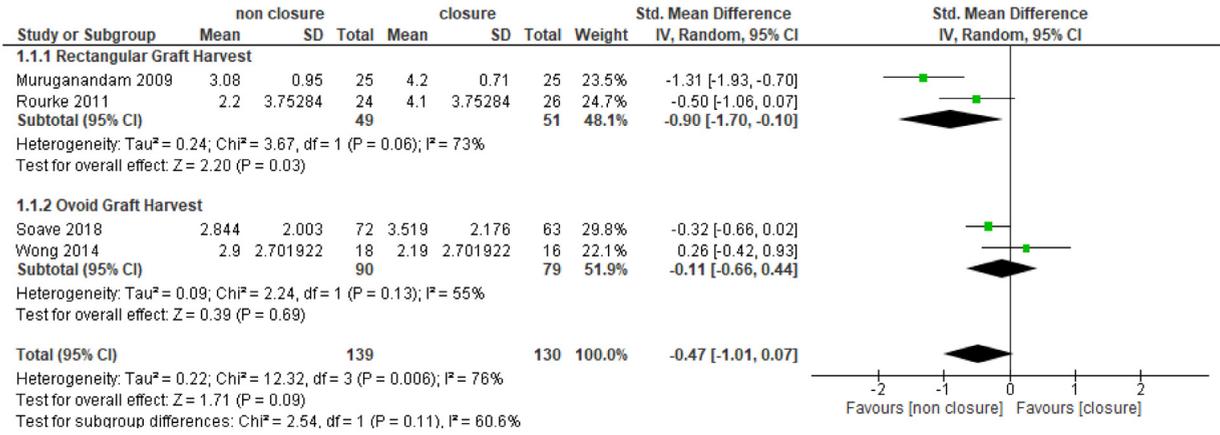
TABLE 1. Summary of randomized controlled trial study characteristics included for the meta-analysis

Author/ Year	Country	Study Design	Sex of Recruited Patients	Indication for BMG	Sex/Indication for BMG/Age	Hemostasis Approach	Buccal Source	Closure Technique/ Sutures	Intraop Anesthesia/ Hydrodistention	Graft Size	Outcome Assessed	The Survey Used for Outcome Assessment	Nonclosure	Closure	Follow-up Duration	Pain Meds or Additional Oral Antiseptics	Remarks
Muruganandam 2009	India	RCT	Not described	all for urethroplasty	Non-closure mean 35 yo (range 18-64), closure mean 35.2 yo (range 17-72)	Bipolar electrocautery, adrenalin-soaked gauze left for 4-6 hrs	Inner cheek and lower lip, rectangular shape	3-0 Vicryl, interlocking continuous suture	local anesthetic 1% Xylocaine and adrenaline solution (1:100000)	Nonclosure Graft area mean 14.9 (range 3.6-30.6); closure Graft area mean 8.6 (range 5.3-18)	Pain score, # with difficult mouth opening, # with perioral numbness, # tolerating liquid day 1, # tolerating diet day 3, salivatory problem and retention cyst	5-point scale visual analog score	N = 25	N = 25	d1, d2, d5, m6	Not described	Reported none of the patients from either group had significant bleeding, hematoma or wound healing problems. Described 1 patient with a mucous retention cyst in donor site closure group with no surgical intervention needed.
Rourke 2012	Canada	RCT	all male patients	all for urethroplasty	Non-closure mean 44.4 yo, closure mean 43.8 yo	Bipolar electrocautery, 2 pieces cottonoid soaked with 1% lidocaine with epinephrine, removed at the end of procedure	Inner cheek, rectangular shape	3-0 Chromic running suture	local anesthetic 1% lidocaine with epinephrine	standardized both group 6cmx2.5cmW	Pain score, interval to regular diet, change in salivation, interval to full mouth opening, the presence of perioral numbness	a validated 10-point numeric pain scale	N = 24	N = 26	d1-d7, m1, m3, m6 (graph). The detailed result only d1, d6, m6	Not described	Reported no major (Clavien grade 2 or greater) perioperative complications occurred in either group with respect to the graft harvest site. No patients experienced a complication due to infection or bleeding.
Wong 2014	UK	RCT	Not described	all for urethroplasty	Overall median 44 yo (23-64); Non-closure median age 41 yo (range 23-59), Closure median 47 yo (range 31-64)	Bipolar diathermy, wet gauze removed prior extubation	left cheek, ovoid shape	4-0 Vicryl Rapide continuous sutures	local anesthetic 20ml 0.25% Marcain with adrenalin (1:200000)	Non closure Graft width mean 2cm, Graft length mean 5+0.9 cm (2-6.5), Graft area mean 7.8 +1.5 cm; Closure graft width mean 2cm, Graft length mean 5.6+0.9 (4.5-7), Graft area mean 8.8 +1.5cm	Pain score, oral fluid, diet, numbness, Tightness	A non validated questionnaire with a 10 point visual analog scale for five parameters	N = 18	N = 16	0, d1, d3, w3, m3, m6, m9, m12	0.2% chlorhexidine digluconate mouth wash after each meal	reported no major bleeding complications, perioral numbness, retention cyst, scar contracture or trismus requires surgical intervention in both treatment groups.
Soave 2018	Germany	RCT	all male patients	all for urethroplasty	Non-closure median 53 yo (IQR 34-66), Closure median 55 (IQR 39-68)	Bipolar electrocautery, one piece cottonoid removed at the end of surgical procedure	Inner cheek, ovoid shape	4-0 Monofil interrupted sutures	local anesthetic 2% lidocaine with adrenaline	Standardized graft width both group 1.5cm; Non-closure Graft length median 4.5 (IQR 4-6), closure median 5 (IQR 5-8)	Pain score, mouth opening impairment, altered taste perception, oral numbness, impaired eating, impaired drinking, oral bleed, impaired smiling, impaired whistling, oral swelling, slurred speech, the burden in daily life due to oral morbidity, oral complication#	The intensity of pain of the oral cavity assessed using a validated uni dimensional single 11-point Numeric Rating Score	N = 72	N = 63	d1, d5, d21, m3, m6	NSAID, paracetamol, combined with a weak opioid, daily oral rinsing with chamomile day 1-5	Reported event rate of Clavien-Dindo category 1 for each treatment groups, none of the cases need further surgical intervention.

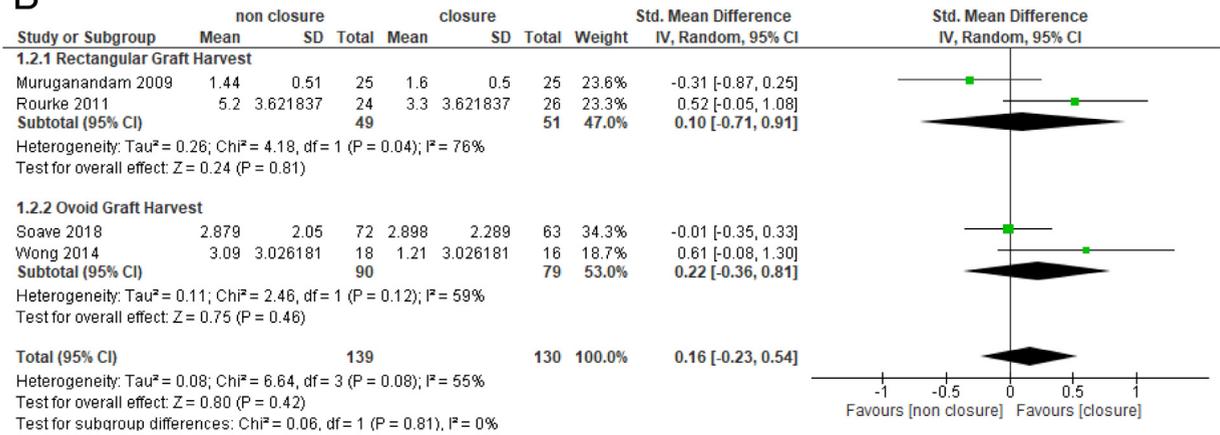
Table 2. Summary of nonrandomized comparative study characteristics included for the systematic review

Author/ Year	Country	Study Design	Sex of Recruited patients	Indication for BMG	Sex/Indication for BMG/Age	Hemostasis Approach	Buccal Source	Closure Technique/ Sutures	Intraop Anesthesia/ Hydrodistention	Graft Size	Outcome Assessed	The Survey Used for Outcome Assessment	Nonclosure	Closure	Follow-up duration	Pain Meds or Additional oral Antiseptics	Remarks
Wood 2004	UK	Prospective cohort	All male patients	All for urethroplasty	All males/overall median age 49yo (range 23-73), nonclosure median 50.5 yo (range 24-70), closure median 50.5 range 26-70)	monopolar diathermy	inner cheek, lower lips	no description	15ml 0.5% xylocaine with 1 in 200,000 adrenalin	no description	Pain score	a 5-point analog pain score	N = 20	N = 20	d1-d5	No description	"Mean daily pain score for patients whose donor site was suture closed was 3.68 versus 2.26 for those whose donor site was left open. In both groups, the pain was maximal on postoperative day 1 and least on postoperative day 5. Mean daily pain score was always higher in the group with donor site closure, and this difference reached statistical significance on postoperative days 4 and 5."
Eeck 2010	Belgium	Considered retrospective comparative study: Survey sent to subjects and answer item assessment as "remembered"	Not described	All for urethroplasty	No description	No description	No description	No description	No description	Mean graft surface 8.7cm (SD 5.05); non- closure 9.19, closure 8.24cm	Postop pain, fluid intake, soft food, and solid food intake. Peri-oral numbness, mouth opening, and salivary flow.	Self-developed questionnaires assessing different outcome parameters	N = 61	N = 30	m6 (mean follow-up 31.4 months SD 20.06)	No description	No significant differences between closure versus non- closure of the graft harvest sites in all parameters assessed.
Steffens 2011	Germany	Described as prospective data for late oral morbidity	Not described	All for urethroplasty	All males/ adults mean age 57 yo, children average 14 yo	No description	Inner cheek and lip mucosa	No description	No description	Average graft length 4.2cm (ranges 2.5- 21cm)	Neurosensory deficit and mouth tightness	Validated oral symptoms questionnaire set	N = 18	N = 38	d21, m12, m36, m84	No description	"The acute oral discomfort disappeared after 3 weeks. Neurosensory deficits and mouth tightness still existed after 84 months in 7 of 56 patients (10.2%). A difference between primary closure and healing by secondary intent did not exist. A neural complication or parotid gland duct obstruction did not occur even in one case of duct orifice resection."
Hölzle 2012	Germany	Prospective cohort	All male patients	All for urethroplasty	No description	No description	Inner cheek, lower lip, rectangular shape	Vicryl 3-0 interrupted sutures.	No description	Overall graft measurement average 5.5 × 3cm (range 1 × 2cm to 2 × 8cm)	Pain score, numbness, and tightness of harvest sight, perfusion and oxygenation parameters of donor site using Doppler flow and tissue spectroscopy.	modified SF-8 questionnaire for the general health condition, questionnaire for outcome assessment not detailed.	N = 5	N = 10	w1, w3, w24	No description	There were no statistically significant differences in the oxygenation and perfusion parameters as well as clinical examination.
Modgil 2014	UK	Considered retrospective: Interviewed 4-5 years after the procedure	Not described	All for urethroplasty	All males/ non- closure mean age 49 yo, closure mean age 45 yo	No description	No description	No description	No description	No description	Pain score, resumption of normal diet, perioral numbness, tightness on mastication, and scar biting	oral pain score assessed using (5 point analogue score, 1 = none to 5 = severe)	N = 19	N = 38	4-5 years post procedure	No description	"There was little difference in mean pain scores between the groups, 1.1 vs. 1.3 respectively. The resumption of a normal diet favored the closure group (10.5% vs. 0%), with less perioral numbness (10.8% vs. 21.1%). Non- closure resulted in a lower incidence of scar biting (15.8% vs. 27%). A greater proportion of patients in the closure group would permit future buccal harvesting (92% vs. 78.9%), and recommend BUMG urethroplasty (97.3% vs. 84.2%)."

A



B



C

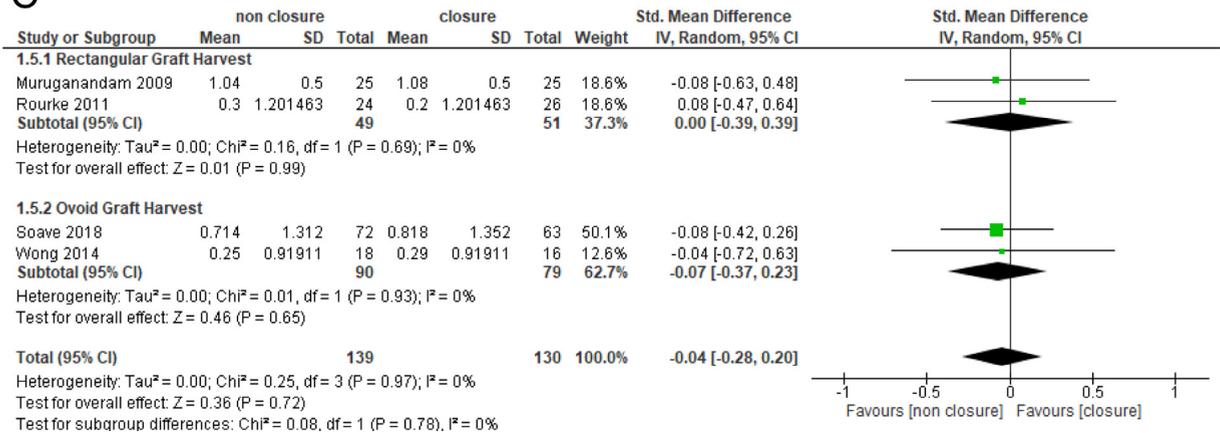


Figure 1. (A) Forest plot pooled effect estimates for outcome of postprocedural day-1 oral pain score; Comparison: Nonclosure vs closure of buccal mucosal graft harvest site. Subgroup: Buccal graft shape (rectangular and oval shape). Statistical method: Inverse Variance with random-effect model (Standardize Mean Difference [SMD] and 95% CI- confidence interval) (B) Forest plot pooled effect estimates for outcome of postprocedural day 3-7 oral pain score; Comparison: Nonclosure vs closure of buccal mucosal graft harvest site. Subgroup: Buccal graft shape (rectangular and oval shape). Statistical method: Inverse Variance with random-effect model (Standardize Mean Difference [SMD] and 95% CI- confidence interval) (C) Forest plot pooled effect estimates for outcome of postprocedural 6 month follow-up oral pain score; Comparison: Nonclosure vs closure of buccal mucosal graft harvest site. Subgroup: Buccal graft shape (rectangular and oval shape). Statistical method: Inverse Variance with random-effect model (Standardize Mean Difference [SMD] and 95% CI- confidence interval). (Color version available online.)



Figure 2. Risk of bias assessment for included randomized controlled trial. (Color version available online.)

of the included studies assessing pain intensity perception at postprocedure day-1, publication bias is not likely to be present.

DISCUSSION

Consistent with the findings of the nonrandomized comparative studies, the result of our meta-analysis on the pain perception and several other outcome parameters assessed shows no significant difference based on closure of the BMG harvest site. However, when subgroup analysis was performed according to the shape of the graft harvested, there are some pooled SMD of continuous outcomes that show statistical significance. According to Cohen's *d* interpretation of effect size, an SMD with more than 0.8 represents a large effect, and a 0.2 difference represents a small effect.¹² Considering this interpretation, the lesser pain perception (SMD -0.90 , 95% CI -1.70 , -0.10) noted at postprocedure day-1 among the nonclosure group of the rectangular shape graft harvested may indeed have some clinical implication. This finding may support the argument of Barbagli and Lazzeri in their 2012 commentary that the shape of the graft harvested may affect pain perception of the patients.¹⁰ Furthermore, in

their later publication, they further illustrated that closing a rectangular mucosal defect may increase tension thereby causing subsequent oral morbidities.²⁶

The pooled effect estimates that showed increased discomfort for oral fluid and solid intake noted in the nonclosure group on postoperative day-1 were only derived from the studies with ovoid BMG. Although there were no studies of rectangular BMG that assessed oral intake; however, these significant findings may correspond to the histologic studies that demonstrated an increased inflammatory process as expressed by tumor necrosis factor-alpha and beta on buccal mucosa healing site immediately postoperatively. This was noted to peak at day 3-5, then declined beyond postprocedure day-7.^{27,28} Similarly, a recently published atlas illustrating the BMG harvest site partially closed using interrupted chromic sutures and a portion left open for secondary healing over 100 days showed that the open wound epithelialized beyond the seventh day postprocedure.²⁹ Furthermore, the transient increased mouth opening discomfort or tightness noted on postoperative day 3-7 in the closure group, mainly noted from the studies that harvested ovoid shaped grafts, may be due to initial suture tension of the closure intraorally. This does

not seem to have a significant effect on long-term oral intake; particularly, this likely accounts for the lack of significance seen at the 6-month follow-up in this group. Despite these immediate post-procedure and short-term differences noted in our meta-analysis, all included comparative studies in this systematic review have reported no difference between groups in long-term assessment of oral morbidity.^{19,22,23,25}

The strengths of this systematic review include a comprehensive literature search for relevant comparative studies that assess the effects of nonclosure vs closure of the BMG harvest sites. However, despite using a sensitive search term to identify all available studies, there is still an innate limitation of our study. Particularly, there are few adequate quality RCT studies available that can be pooled to generate an effect estimate for inference of intended outcome of assessment. Subgroup analyses for age, sex, or other surgical techniques were not feasible either due to no available trials or lack of detailed description in the studies. To date, there was no available pediatric study that assessed the subject topic, and all the included studies only assessed inner cheek BMG harvest site. Hence, the generated effect estimate from our review could not be inferred for pediatric population or for harvest sites such as lingual or labial. Furthermore, the perioral numbness and other potentially long-lasting complications may not be adequately assessed, since the included RCTs have a relatively short duration of follow-up. The nonrandomized comparative studies were either dated or too preliminary to be included for meta-analysis.

The available overall quality of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation criteria³⁰ is considered to be very low to low quality to generate any recommendation. The high risk of bias in the study domains and presence of moderate to considerable heterogeneity have led to downgrading for risk of bias, heterogeneity, inconsistency, and imprecision. We therefore recommend further high-quality studies to further assess, validate and strengthen the evidence generated from this review; specifically, with consideration of graft shape and graft size as intervening variables on the effect of closure versus nonclosure of the BMG harvest site.

CONCLUSION

The current evidence suggests no significant difference for postprocedural pain perception of the patient between closure and nonclosure of the BMG harvest site. However, it seems that the shape of the BMG graft can be a factor that may lead to increased short-term postprocedural pain. Specifically, the nonclosure rectangular BMG harvest site appears to slightly decrease immediate post-procedure pain intensity reporting. There is very low evidence to suggest any large effect of closure vs nonclosure of BMG harvest site on postprocedural mouth opening tightness or oral intake impairment.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.urology.2018.12.008>.

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