Original Article
Prostate diseases and male voiding dysfunctions

pISSN: 2287-4208 / eISSN: 2287-4690
World J Mens Health 2022 Jan 40(1): 116-126
https://doi.org/10.5534/wjmh.200175

The World Journal of MEN's HEALTH

A Systematic Review of Randomized Controlled Trials Comparing Buccal Mucosal Graft Harvest Site Non-Closure *versus* Closure in Patients Undergoing Urethral Reconstruction

Eu Chang Hwang[1], Adam de Fazio[2], Kallie Hamilton[3], Caitlin Bakker[4], Joseph J. Pariser[2], Philipp Dahm[2,3]

[1]*Department of Urology, Chonnam National University Medical School, Hwasun, Korea,* [2]*Department of Urology, University of Minnesota,* [3]*Minneapolis VA Health Care System, Specialty Care,* [4]*Health Sciences Libraries, University of Minnesota, Minneapolis, MN, USA*

Purpose: To assess the effects of buccal mucosal graft site non-closure *versus* closure on postoperative oral morbidity for male undergoing augmentation urethroplasty for urethral stricture.

Materials and Methods: We included randomized controlled trials. Inclusion criteria were male over the age of 18 with urethral stricture disease requiring reconstruction with buccal mucosal graft harvest. Primary outcomes of the review were postoperative oral pain, need for secondary oral procedures and cosmetic defects.

Results: We included 5 studies with 346 randomized patients with urethral strictures, of whom 260 completed the trials. In terms of primary outcomes, non-closure graft site may reduce oral pain on postoperative day #1 (standard mean difference [SMD] 0.24 lower; 95% confidence interval [CI] 0.61 lower to 0.12 higher; low certainty evidence [CoE]) but we are uncertain how this impacts pain on postoperative days 3 to 6 (SMD 0.35; 95% CI 0.12 to 0.81 higher; very low CoE). We are also very uncertain as to how it affects the need for secondary oral procedures (risk ratio [RR] 0.22; 95% CI 0.01 to 4.28; very low CoE). Non-closure may increase the risk of cosmetic defects (RR 2.40; 95% CI 0.93 to 6.22; low CoE).

Conclusions: This review describes the trade-off for buccal mucosal graft site non-closure *versus* closure for various patient-important outcomes; decision-making will likely hinge on the relative value individual patients and surgeons place on them. The supporting evidence was rated as low and very low, thereby signaling substantial underlying uncertainty and the need for better trials.

Keywords: Mouth mucosa; Systematic review; Transplants; Urethral stricture

INTRODUCTION

Urethral stricture disease refers to any abnormal narrowing of the urethral segment. This is a relatively common disease in male with an associated prevalence of 229–627 per 100,000 males, or 0.6% of the at-risk

Received: Oct 2, 2020 **Revised:** Dec 11, 2020 **Accepted:** Dec 25, 2020 **Published online** Feb 15, 2021
Correspondence to: Philipp Dahm https://orcid.org/0000-0003-2819-2553
Minneapolis VA Health Care System, Urology Section 112D, One Veterans Drive, Minneapolis, MN 55417, USA.
Tel: +1-612-467-3532, **Fax:** +1-612-467-2232, **E-mail:** pdahm@umn.edu

population, who are typically older male. Data from Medicare and Medicaid Services (for patients older than 65 years) confirmed an increased incidence of stricture disease at 9.0/100,000 for 2001 compared to 5.8/100,000 in patients younger than 65 years [1]. Although many strictures are idiopathic, common causes factors include urethral instrumentation, gonorrhea, lichen sclerosus, trauma, and radiation [2]. Treatment options include both endourologic interventions (*e.g*., dilation or urethrotomy) and urethroplasty. The technique for urethroplasty is somewhat surgeon dependent but primarily depends on the location, length and recurrent nature of the stricture. The American Urological Association (AUA) Guideline on Male Urethral Stricture suggests urethroplasty as the preferred intervention for 1) recurrent or complicated strictures of the meatus/fossa, 2) all strictures of the penile urethra, and 3) long (>2 cm) or recurrent strictures of the bulbar urethra [3]. Some urethral strictures, especially longer ones or those located in the pendulous urethra, necessitate the use of graft during the repair. Buccal mucosa is the most commonly used graft as it is hairless, readily harvested, and has a thin lamina propria. There are varied practice patterns regarding closure or non-closure of the buccal graft harvest site. Many surgeons perform closure of the oral graft harvest site fashion as a standard component of the procedure [4,5]. However, several observational studies suggested that oral mucosa harvest site non-closure may result in decreased oral pain and morbidity [6-8], but this remains controversial. In this review, we, therefore, assessed the effects of buccal mucosal graft site non-closure *versus* closure on postoperative oral morbidity for male undergoing augmentation urethroplasty for urethral stricture to help inform clinicians and guideline developers.

MATERIALS AND METHODS

This systematic review and meta-analysis was based on a priori registered protocol (PROSPERO: CRD42018105344 from 8/14/2018). A trained medical librarian (CB) performed electronic searches of the Cochrane Central Register of Controlled Trials via Wiley, Medline and Embase via Ovid, Web of Science Core Collection, Scopus, Global Index Medicus, ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP) from their inception through to March 12, 2020 regardless of their publication status or language of publication (Supplement Table 1-4). We also searched the references of full articles retrieved for our review to identify any additional studies. All steps were performed independently and in duplicate in accordance with our protocol using the Covidence software platform (www.covidence.org). We included participants over the age of 18 with urethral stricture disease requiring reconstruction with buccal mucosal graft harvest. We excluded studies conducted in adolescents, children, female. We compared buccal mucosa graft harvest site non-closure *versus* closure. Primary outcomes of the review were postoperative oral pain (assessed with visual analogue scale or numerical rating scale, time point of measurement: up to postoperative day 6), need for secondary oral procedures (*e.g*., repair of bleeding or contracture, time point of measurement: up to 12 months) and cosmetic defects (*e.g*., impaired smiling, time point of measurement: up to 6 months), while secondary outcomes were oral numbness (time point of measurement: up to 6 months), salivary problems (salivary duct problem, time point of measurement: up to 4 weeks), impaired mouth opening (time point of measurement: up to 4 weeks), delayed oral intake (time point of measurement: up to postoperative day 6) and infection (clinical features with patient started on antibiotics, time point of measurement: up to 6 months). We considered an standardized mean difference (SMD) 0.2 as a clinically important difference for continuous outcomes and a relative risk reduction of at least 25% as a clinically important difference for categorical outcomes.

Two review authors (AD, PD) independently assessed the risk of bias of each included study. We resolved all disagreements by discussion and consensus. Any disagreements were reconciled by a third team member. We assessed risk of bias using the Cochrane 'Risk of bias' tool. We judged risk of bias domains as 'low risk', 'high risk', or 'unclear risk' and evaluated individual bias items as described in the Cochrane Handbook for Systematic Reviews of Interventions [9]. Review authors working in pairs (AD, KP) independently extracted data using a previously tested standardized form. Any disagreements were reconciled by a third team member. We summarized data using a random-effects model. We used Review Manager 5.3 software (Cochrane Collaboration, Copenhagen, Denmark) to perform the statistical analyses. We planned to carry out subgroup analyses with investigation of interaction

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for bilateral graft harvest (bilateral *versus* unilateral), graft closure technique (running *versus* interrupted) and use of fulguration with non-closure (fulguration *versus* non-fulguration) but were unable to do so. We performed a post hoc sensitivity analyses by adding two pseudo-randomized controlled trials we identified. We rated the certainty of evidence (CoE) on a per outcome basis using GRADE, which takes into account five criteria related to internal validity (risk of bias, inconsistency, imprecision, publication bias), and external validity, such as directness of results [10]. For each comparison, two review authors (ECH, PD) independently rated the certainty of evidence for each outcome as 'high', 'moderate', 'low' or 'very low' using the GRADEpro software (www.gradepro.org). We resolved any discrepancies by consensus. We used GRADE guidance to describe both the certainty of evidence and the magnitude of the effect size [11].

Ethics statement

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and AMSTAR 2 Check list. This study was ethical approval is unnecessary.

RESULTS

Our search yielded 1,275 records. After removal of duplicates, we screened the titles and abstracts of 590 records, excluded 564 and then screened 26 full-text articles of which we excluded 15 references [12-26], which did not meet our inclusion criteria; see PRISMA flowchart (Fig. 1) for further details. We identified one ongoing trial [26]. In all, 5 studies informed by 11 references (including abstracts) were included in the qualitative and quantitative synthesis of this review [27-31].

1. Description of included studies

We included 5 studies with 346 randomized patients with urethral strictures, of whom 260 completed the trials. All patients underwent unilateral buccal mucosa graft harvest for augmentation urethroplasty with the harvest site non-closure or closure. The studies were performed in Canada [27], the United Kingdom [28], Germany [29] and India [30,31]. The age range of participants was 35 to 55 years. Three studies included participants with either penile or bulbar urethral strictures [29-31]; one study only included participants with bulbar strictures [27], and one study made no reference to stricture location [28]. Four studies [27-29,31] used buccal mucosa and one study used lingual mucosa graft

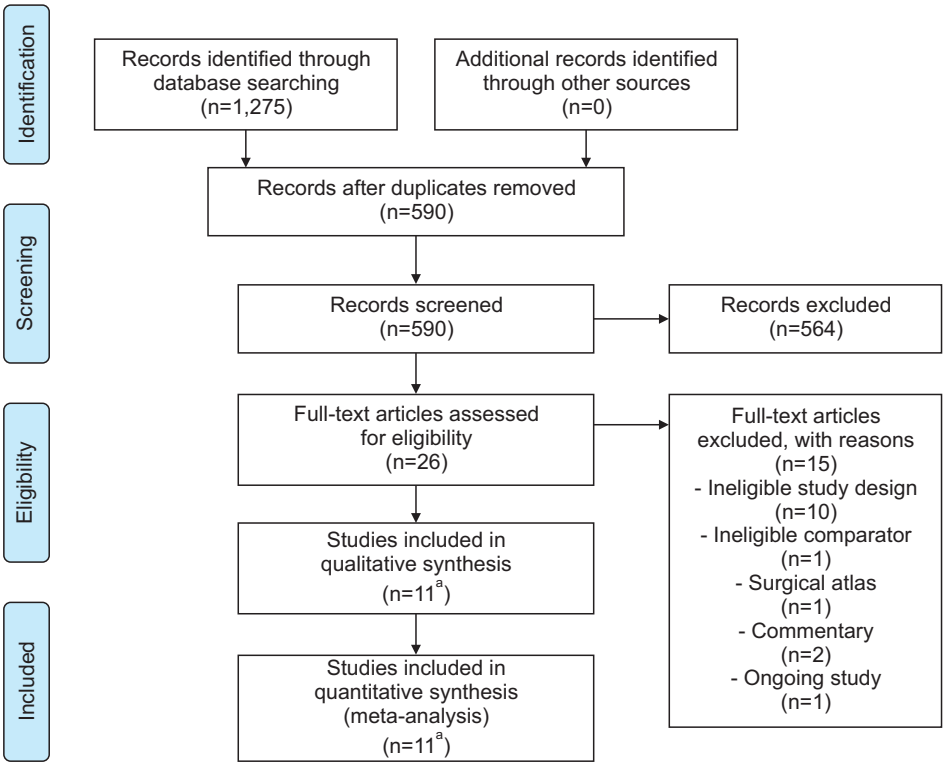

Fig. 1. PRISMA diagram for the study selection process. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses. [a]The total number of included references is 11 mappings to 5 unique studies.

[30]. In four studies, graft harvest was preceded by buccal infiltration with varying local anesthetics (0.25% marcaine with epinephrine, [28]; 1.0% lidocaine with epinephrine, [27]; 2% lidocaine with epinephrine, [29]; 1% xylocaine and adrenaline [31]). Standardized graft shape was ovoid in two studies [28,29] and rectangular in one study [27]. Graft shape was not mentioned in two studies [30,31] Closure techniques and suture choice varied between studies with three studies employing continuous closure [27,28,31] and two studies using interrupted suture [29,30]. Three studies [29-31] specified no source of funding while the two other studies [27,28] made no mention of funding sources. Four studies [27,28,30,31] specified no conflicts of interest while one made no mention of conflicts [27]. Supplement Table 1 provides additional details of the included studies.

All included studies had an unclear or high risk of bias across several domains [27-31] potentially susceptible to selection bias, performance bias, detection bias, and attrition bias. Regarding selection bias, two studies [30,31] used quasi-randomization method. Based on our protocol, they were initially excluded but then considered in a post hoc sensitivity analysis. Fig. 2 summarizes the risk of bias assessment for each study. The summary of findings for the entire body of evidence is detailed in Table 1 and 2. We were unable to conduct preplanned sensitivity analyses and subgroup analyses stratified by laterality of graft harvest and use of fulguration due to a lack of relevant data in the included studies.

Fig. 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

2. Main analysis based on randomized trials (excluding two quasi-randomized trials)

1) Oral pain on postoperative day #1

Based on 3 randomized trials reporting this outcome [27-29], non-closure of the buccal mucosa graft harvest site may reduce oral pain slightly compared to closure (SMD: -0.24, 95% CI: -0.61 to 0.12, I^2=34%, low CoE; Table 1, Supplement Fig. 1). We downgraded the CoE for risk of bias and imprecision. Subgroup analysis stratified by graft closure technique showed that the test for interaction was not significant (p=0.67, I^2=0%; Supplement Fig. 1).

2) Oral pain on postoperative day #3 to 6

The evidence is very uncertain about the effect of non-closure of the buccal mucosa graft harvest site on oral pain compared to closure (SMD: 0.35, 95% CI: -0.12 to 0.81, I^2=56%, very low CoE; Table 1, Supplement Fig. 2). We downgraded the CoE for risk of bias, imprecision and inconsistency. Subgroup analysis stratified by graft closure technique showed that the test for interaction was significant (p=0.03, I^2=78.2%; Supplement Fig. 2).

3) Need for secondary oral procedures

Based on two studies [27,28] with 6 to 12 months follow up, we are very uncertain how non-closure of the buccal mucosa graft harvest site effects the need for secondary oral procedures slightly compared to closure (risk ratio [RR]: 0.22, 95% CI: 0.01 to 4.28, I^2=not applicable, very low CoE; Table 1, Supplement Fig. 3). This corresponds to 37 fewer need for secondary oral procedures (95% CI 47 fewer to 156 more) per 1,000 non-closure participants. We downgraded the CoE for risk of bias and twice for very serious imprecision.

4) Cosmetic defects

Based on one study [29] with 6 months follow up, non-closure of the buccal mucosa graft harvest site may increase cosmetic defects slightly compared to closure (RR: 2.40, 95% CI: 0.93 to 6.22, I^2=not applicable,

Table 1. Non closure of the buccal mucosa graft harvest site compared to closure for urethroplasty using buccal mucosa graft

Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with closure*	Risk difference with non closure
Oral pain (postoperative day 1) Assessed with: 1 study: 11-point NRS, 2 studies: 10-point VAS (high score indicate worse pain)	199 (3 RCTs: Rourke et al, 2012 [27]; Wong et al, 2014 [28]; Soave et al, 2018 [29])	⊕⊕◯◯ LOW[a,b]	-	-	SMD 0.24 lower (0.61 lower to 0.12 higher)
Oral pain (postoperative day 3 to 6) Assessed with: 1 study: 11-point NRS, 2 studies: 10-point VAS (high score indicate worse pain) Follow-up: median 4.5 days	199 (3 RCTs: Rourke et al, 2012 [27]; Wong et al, 2014 [28]; Soave et al, 2018 [29])	⊕◯◯◯ VERY LOW[a,b,c]	-	-	SMD 0.35 higher (0.12 lower to 0.81 higher)
Need for secondary oral procedures Follow-up: range 6 to 12 months	84 (2 RCTs: Rourke et al, 2012 [27]; Wong et al, 2014 [28])	⊕◯◯◯ VERY LOW[a,d]	RR 0.22 (0.01 to 4.28)	48 per 1,000	37 fewer per 1,000 (47 fewer to 156 more)
Cosmetic defects Follow-up: 6 months	84 (1 RCT: Soave et al, 2018 [29])	⊕⊕◯◯ LOW[a,e]	RR 2.40 (0.93 to 6.22)	119 per 1,000	167 more per 1,000 (8 fewer to 621 more)
Oral numbness Follow-up: 6 months	134 (2 RCTs: Rourke et al, 2012 [27]; Soave et al, 2018 [29])	⊕◯◯◯ VERY LOW[a,f,g]	RR 0.89 (0.38 to 2.06)	529 per 1,000	58 fewer per 1,000 (328 fewer to 561 more)
Salivary problems (postoperative day 1)	116 (1 RCT: Soave et al, 2018 [29])	⊕⊕◯◯ LOW[a,g]	RR 1.09 (0.78 to 1.53)	519 per 1,000	47 more per 1,000 (114 fewer to 275 more)
Impaired mouth opening (postoperative 3 to 4 weeks) Follow-up: range 3 to 4 weeks	164 (2 RCTs: Rourke et al, 2012 [27]; Soave et al, 2018 [29])	⊕⊕◯◯ LOW[a,h]	RR 0.86 (0.68 to 1.08)	551 per 1,000	77 fewer per 1,000 (176 fewer to 44 more)
Delayed oral intake (postoperative day 1)	162 (2 RCTs: Rourke et al, 2012 [27]; Soave et al, 2018 [29])	⊕◯◯◯ VERY LOW[a,i,j]	RR 0.64 (0.18 to 2.30)	831 per 1,000	299 fewer per 1,000 (682 fewer to 1,081 more)
Delayed oral intake (postoperative day 3 to day 6) Follow-up: median 4.5 days	164 (2 RCTs: Rourke et al, 2012 [27]; Soave et al, 2018 [29])	⊕◯◯◯ VERY LOW[a,f,g]	RR 0.87 (0.44 to 1.73)	603 per 1,000	78 fewer per 1,000 (337 fewer to 440 more)
Infection Follow-up: 6 months	50 (1 RCT: Rourke et al, 2012 [27])	⊕◯◯◯ VERY LOW[a,k]	Not estimable	Not estimable	Not estimable

Patient or population: men with urethral stricture undergoing urethroplasty using buccal mucosa graft. Setting: inpatients/Canada, Germany, United Kingdom. Intervention: non closure of the buccal mucosa graft harvest site. Comparison: closure of the buccal mucosa graft harvest site. GRADE Working Group grades of evidence: high certainty, we are very confident that the true effect lies close to that of the estimate of the effect; moderate certainty, we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low certainty, our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; very low certainty, we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

CI: confidence interval, NRS: numerical rating scale, RR: risk ratio, SMD: standardised mean difference, VAS: visual analogue scale, RCT: randomized controlled trial.

[a]Downgraded by one level for study limitations: high risk or unclear risk in several domains.

[b]Downgraded by one level for imprecision: wide confidence interval crosses no effect and assumed threshold of clinically important difference (SMD: 0.2).

[c]Downgraded by one level for inconsistency: moderate heterogeneity.

[d]Downgraded by two levels for imprecision: very wide confidence interval.

[e]Downgraded by one level for imprecision: confidence interval crosses no effect and assumed threshold of clinically important difference (relative risk increase of at least 25%).

[f]Downgraded by one level for inconsistency: substantial heterogeneity.

[g]Downgraded by one level for imprecision: wide confidence interval.

[h]Downgraded by one level for imprecision: confidence interval crosses no effect and assumed threshold of clinically important difference (relative risk reduction of at least 25%).

[i]Downgraded by two levels for inconsistency: considerable heterogeneity.

[j]We did not downgrade for imprecision because wide confidence interval results from inconsistency.

[k]Downgraded by two levels for imprecision: no events.

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Table 2. Non closure of the buccal/lingual mucosa graft harvest site compared to closure for urethroplasty using buccal/lingual mucosa graft

Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with closure*	Risk difference with non closure
Oral pain (postoperative day 1) Assessed with: 1 study: 11-point NRS, 2 studies: 10-point VAS, 1 study: non validated scale (high score indicate worse pain)	249 (4 RCTs: Muruganandam et al, 2009 [31]; Rourke et al, 2012 [27]; Wong et al, 2014 [28]; Soave et al, 2018 [29])	⨁⨁◯◯ VERY LOW[a,b,c]	-	-	SMD 0.37 SD lower (0.75 lower to 0.01 higher)
Oral pain (postoperative day 3 to day 6) Assessed with: 1 study: 11-point NRS, 3 studies: 10-point VAS, 1 study: non validated scale (high score indicate worse pain) Follow-up: median 4.5 days	291 (5 RCTs: Gulani et al, 2019 [30]; Muruganandam et al, 2009 [31]; Rourke et al, 2012 [27]; Wong et al, 2014 [28]; Soave et al, 2018 [29])	⨁◯◯◯ VERY LOW[a,b,c]	-	-	SMD 0.08 SD higher (0.3 lower to 0.47 higher)
Oral numbness Follow-up: 6 months	226 (4 RCTs: Gulani et al, 2019 [30]; Muruganandam et al, 2009 [31]; Rourke et al, 2012 [27]; Soave et al. 2018 [29])	⨁◯◯◯ VERY LOW[a,b,d]	RR 0.86 (0.42 to 1.77)	333 per 1,000	47 fewer per 1,000 (193 fewer to 257 more)
Salivary problems (postoperative day 1)	166 (2 RCTs: Muruganandam et al, 2009 [31]; Soave et al, 2018 [29])	⨁◯◯◯ VERY LOW[a,b,d]	RR 0.65 (0.11 to 3.96)	392 per 1,000	137 fewer per 1,000 (349 fewer to 1,162 more)
Delayed oral intake (postoperative day 1)	212 (3 RCTs: Muruganandam et al, 2009 [31]; Rourke et al, 2012 [27]; Soave et al, 2018 [29])	⨁◯◯◯ VERY LOW[a,d,e]	RR 0.61 (0.20 to 1.92)	647 per 1,000	252 fewer per 1,000 (518 fewer to 595 more)
Delayed oral intake (postoperative day 3 to 6) Follow-up: median 4.5 days	256 (4 RCTs: Gulani et al, 2019 [30]; Muruganandam et al, 2009 [31]; Rourke et al, 2012 [27]; Soave et al, 2018 [29])	⨁◯◯◯ VERY LOW[a,b,d]	RR 0.66 (0.31 to 1.39)	452 per 1,000	154 fewer per 1,000 (312 fewer to 176 more)

Patient or population: men with urethral stricture undergoing urethroplasty using buccal/lingual mucosa graft. Setting: inpatients/Canada, Germany, United Kingdom, India. Intervention: non closure of the buccal/lingual mucosa graft harvest site. Comparison: closure of the buccal/lingual mucosa graft harvest site. GRADE Working Group grades of evidence: high certainty, we are very confident that the true effect lies close to that of the estimate of the effect; moderate certainty, we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low certainty, our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

CI: confidence interval, NRS: numerical rating scale, RR: risk ratio, SMD: standardised mean difference, VAS: visual analogue scale, RCT: randomized controlled trial.

[a]Downgraded by one level for study limitations: high risk or unclear risk in several domains.

[b]Downgraded by one level for inconsistency: moderate heterogeneity.

[c]Downgraded by one level for imprecision: wide confidence interval crosses no effect and assumed threshold of clinically important difference (SMD: 0.2).

[d]Downgraded by one level for imprecision: wide confidence interval.

[e]Downgraded by one level for inconsistency: substantial heterogeneity.

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

low CoE; Table 1, Supplement Fig. 4). This corresponds to 167 more cosmetic defects (95% CI 8 fewer to 621 more) per 1,000 non-closure participants. We downgraded the CoE for risk of bias and imprecision.

5) Oral numbness

Based on two studies [27,29] with 6 months follow up, the evidence is very uncertain about the effect of non-closure of the buccal mucosa graft harvest site on oral numbness compared to closure (RR: 0.89, 95% CI: 0.38 to 2.06, I^2=74%, very low CoE; Table 1, Supplement Fig. 5). We downgraded the CoE for risk of bias, imprecision and inconsistency.

6) Salivary problems

Based on one study [29] based on postoperative day 1, non-closure of the buccal mucosa graft harvest site may increase salivary problems slightly compared to closure (RR: 1.09, 95% CI: 0.78 to 1.53, I^2=not applicable, low CoE; Table 1, Supplement Fig. 6). This corresponds to 47 more salivary problems (95% CI 114 fewer to 275 more) per 1,000 non-closure participants. We downgraded the CoE for risk of bias and imprecision.

7) Impaired mouth opening

Based on two studies [27,29] with data from postoperative weeks 3 to 4, non-closure of the buccal mucosa graft harvest site may reduce impaired mouth opening compared to closure. (RR: 0.86, 95% CI: 0.68 to 1.08, I^2=0%, low CoE; Table 1, Supplement Fig. 7). This corresponds to 77 fewer impaired mouth opening (95% CI 176 fewer to 44 more) per 1,000 non-closure participants. We downgraded the CoE for risk of bias and imprecision.

8) Delayed oral intake on postoperative day #1

Based on two studies [27,29], the evidence is very uncertain about the effect of non-closure of the buccal mucosa graft harvest site on delayed oral intake compared to closure (RR: 0.64, 95% CI: 0.18 to 2.30, I^2=93%, very low CoE; Table 1, Supplement Fig. 8). We downgraded the evidence CoE for risk of bias and inconsistency (two levels).

9) Delayed oral intake on postoperative day #3 to 6

Based on two studies [27,29], the evidence is very uncertain about the effect of non-closure of the buccal mucosa graft harvest site on delayed oral intake compared to closure (RR: 0.87, 95% CI: 0.44 to 1.73, I^2=59%, very low certainty evidence; Table 1, Supplement Fig. 9). We downgraded the CoE for risk of bias, imprecision and inconsistency.

10) Infection

Based on one study [27] the evidence is very uncertain about the effect of non-closure of the buccal mucosa graft harvest site on the infection. We downgraded the CoE for risk of bias and imprecision (two levels).

3. Sensitivity analyses

We performed additional post hoc analysis to include the two pseudo-randomized controlled trials [30,31] our search identified. The results did not substantially change the results and/or lowered the certainty of evidence. Details of this analysis are reported in the Appendix (Supplement Fig. 10-15).

DISCUSSION

1. Statement of principal findings

We identified three randomized controlled trials that have addressed the topic of buccal mucosa graft harvest site all of which had important methodological limitations that negatively impacted the confidence we can place it this body of evidence. In terms of desirable effects of non-closure, oral pain on postoperative day #1 and oral numbness may be slightly reduced. Impaired mouth opening on postoperative weeks #3 to #4 may be moderately decreased. In terms of undesirable effects, salivary problems on postoperative day #1 may be slightly increased and cosmetic defects at 6 months may be greatly increased. All of these outcomes were rated as low certainty of evidence. We are very uncertain about the outcomes of the need for secondary oral procedures, oral pain on postoperative days #3–6, oral numbness, and delayed oral intake on postoperative day #1 and days #3–6 and the risk of infection, which were all rated as being informed by evidence of very low certainty.

2. Strengths and weaknesses of the study

Strengths of this review relates to its rigorous methodology, which include a prospectively registered, written protocol, a comprehensive literature search developed and executed by an experienced information specialist, study selection, data abstraction and

certainty of evidence rating using GRADE independently and in duplicate and a contextualized interpretation of outcomes considering both relative and absolute effect size estimates. We also reached out to the studies' principal investigators to obtain additional information not provided in the published manuscript. Limitations relate largely to the quality and quantity of evidence supporting its findings. All studies lacked methodological safeguards against bias and frequently provided inconsistent and/or imprecise results, which prompted additional rating down of the certainty of evidence. Individual studies had small sample sizes and were heterogeneous in terms of type of graft and its shape, anesthetic technique and method of closure; all of these potentially have very important implications on patients' outcomes. Which outcomes were reported and how and when they were assessed also differed, all making it difficult to make generalizations and contributing to low certainty of evidence ratings.

3. Strengths and weaknesses in relation to other studies, discussing important differences in results

Prior systematic reviews have been published on this topic; however, none to date has applied the same rigorous methodology as this study. The most recently published systematic review by Chua et al [32] stands out favorably for its prospective registration in the PROSPERO registry. However, the study did not rate the certainty of evidence on a per outcome basis and presented only relative effect size measure which it interpreted based statistical significance rather than clinically meaningful differences. In contrast, here we qualify each result with a GRADE certainty of evidence rating and place the resulting absolute effect sizes into clinical context. As a result, our study provides a more nuanced presentation of the likely tradeoffs of non-closure *versus* closure. Our study also differs in its focus on randomized controlled trials. This appears justified by the mostly retrospective nature of these comparative studies, small sample size and lack of efforts to adjust for likely confounding by statistical means. These studies appear unlikely to have raised the certainty of evidence, which would have been a potential justification for their inclusion. Regardless, we believe that the indiscriminate pooling of randomized and non-randomized studies in the systematic review by Chua et al [32], is not advisable.

4. Meaning of the study: possible explanations and implications for clinicians and policymakers

This study provides the current best evidence of the trade-offs faced by surgeons and their patients when it comes to decision-making about graft site closure or not. As such, it could become the foundation for shared decision-making tool for surgeons and patients. It should be noted that most observed differences between the two approaches very relatively small and impacted mostly short-term outcomes with the exception of oral numbness and cosmetic defects both at 6 months. Decision-making may therefore hinge on how patients (and their surgeons) value a certain outcome. For example, if a patient was to prioritize avoiding mouth contracture over all other outcomes, non-closure might be preferred.

5. Unanswered questions and future research

Despite three randomized trials addressing this topic, the certainty of evidence for all outcome is either low or very low, highlighting relevant shortcomings in these trials to implement general methodological safeguards against bias such as allocation concealment and blinding of outcome assessors. If there are to be future trials, these should also include a registered protocol, use validated questionnaires to assess patient important outcomes and also anticipate the need for subgroup analyses, for example based on graft size. Future studies should also strive to capture and report the severity and bother of treatment related side-effects such cosmetic defects and salivary issues. An ideal study could be conducted in patients with large urethral defects requiring bilateral graft harvest. The left and the right sides could then be randomized to closure or non-closure, thereby allowing the patient to serve as his own matched controlled. However, patients requiring such large grafts are relatively uncommon making this a challenging trial to complete.

CONCLUSIONS

This review describes the trade-offs for buccal mucosal graft site non-closure *versus* closure for various patient-important outcomes; decision-making will likely hinge on the relative value individual patients and surgeons place on them. The supporting evidence was rated as low and very low, thereby signaling substan-

tial underlying uncertainty; the true effects may be substantially different than these results. There is an important need for better quality trials focusing on patient-important outcomes preferably assessed using validated instruments.

ACKNOWLEDGEMENTS

This study was supported by a grant (HCRI20003) of the Chonnam National University Hwasun hospital Research Institute of Clinical Medicine.

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: ECH, AF. Data curation: AF, KH. Formal analysis: ECH, AF. Methodology: ECH, PD, CB. Writing original draft: ECH. Review & editing: JJP. Supervision: PD.

Supplementary Materials

Supplementary materials can be found *via* https://doi.org/10.5534/wjmh.200175.

REFERENCES

1. Alwaal A, Blaschko SD, McAninch JW, Breyer BN. Epidemiology of urethral strictures. Transl Androl Urol 2014;3:209-13.
2. Lumen N, Hoebeke P, Willemsen P, De Troyer B, Pieters R, Oosterlinck W. Etiology of urethral stricture disease in the 21st century. J Urol 2009;182:983-7.
3. Bayne DB, Gaither TW, Awad MA, Murphy GP, Osterberg EC, Breyer BN. Guidelines of guidelines: a review of urethral stricture evaluation, management, and follow-up. Transl Androl Urol 2017;6:288-94.
4. Bürger RA, Müller SC, el-Damanhoury H, Tschakaloff A, Riedmiller H, Hohenfellner R. The buccal mucosal graft for urethral reconstruction: a preliminary report. J Urol 1992;147:662-4.
5. el-Kasaby AW, Fath-Alla M, Noweir AM, el-Halaby MR, Zakaria W, el-Beialy MH. The use of buccal mucosa patch graft in the management of anterior urethral strictures. J Urol 1993;149:276-8.
6. Jang TL, Erickson B, Medendorp A, Gonzalez CM. Comparison of donor site intraoral morbidity after mucosal graft harvesting for urethral reconstruction. Urology 2005;66:716-20.
7. Kamp S, Knoll T, Osman M, Häcker A, Michel MS, Alken P. Donor-site morbidity in buccal mucosa urethroplasty: lower lip or inner cheek? BJU Int 2005;96:619-23.
8. Wood DN, Allen SE, Andrich DE, Greenwell TJ, Mundy AR. The morbidity of buccal mucosal graft harvest for urethroplasty and the effect of nonclosure of the graft harvest site on postoperative pain. J Urol 2004;172:580-3.
9. Higgins JPT, Altman DG, Sterne JAC. Assessing risk of bias in included studies. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS, editors. Cochrane handbook for systematic reviews of interventions. version 5.2.0. London: Cochrane; 2017.
10. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? BMJ 2008;336:995-8.
11. Santesso N, Glenton C, Dahm P, Garner P, Akl EA, Alper B, et al. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. J Clin Epidemiol 2020;119:126-35.
12. Alsikafi NF, Karapetian A, Elliott SP, McAninch JW. The versatility of buccal grafts in the treatment of urethral stricture disease. J Urol 2004;171(4 Suppl):63-4.
13. Barbagli G, Sansalone S, Kulkarni SB, Romano G, Lazzeri M. Dorsal onlay oral mucosal graft bulbar urethroplasty. BJU Int 2012;109:1728-41.
14. Chapple CR. Oral pain and morbidity with buccal mucosa grafts for substitution urethroplasty: closure or not. Eur Urol 2018;73:923-4.
15. Eeckt KV, Joniau S. Postoperative morbidity of closure versus non-closure of the buccal mucosa harvest site. J Urol 2010;183(4 Suppl):e27.
16. Hölzle F, Mitchell DA, Rau A, Palisaar J, Loeffelbein DJ, Noldus J, et al. Assessment of the perfusion and morbidity of the buccal mucosal donor site for grafting of urethral strictures. J Craniomaxillofac Surg 2012;40:47-50.
17. Jamal JE, Kellner DS, Fracchia JA, Armenakas NA. A randomized prospective trial of primary versus AlloDerm closure of buccal mucosal graft harvest site for substitution urethroplasty. Urology 2010;75:695-700.
18. Universitaire Ziekenhuizen Leuven. Functional outcome of urethral reconstructive surgery [Internet]. Bethesda (MD): U.S. National Library of Medicine; c2019 [cited 2019 Dec 15]. Available from: https://ClinicalTrials.gov/show/NCT01982136.
19. Modgil V, Gill J, Vadukul P, Wharton IP, Anderson PCB.

Long-term patient reported outcome of bothersome oral symptoms following Buccal Mucosal Graft (BUMG) harvest for urethral reconstruction. BJU Int 2014;113(5 Suppl):55.
20. Morey AF. A randomized prospective trial of primary versus AlloDerm closure of buccal mucosal graft harvest site for substitution urethroplasty. J Urol 2010;184:997.
21. Schultz A, Talseth T, Hedlund H. Urethroplasty in urethral strictures. Scand J Urol Nephrol Suppl 2003;37:28-9.
22. Singh KR, Vasudevan S, Praveen G, Rakesh, Narayan, Sunil. Assessment of donor site morbidity of buccal mucosa graft. Indian J Urol 2018;34 Suppl 1:26.
23. Steffens J, Stasczak M, Anheuser P. Late oral morbidity of oral mucosal graft harvest site for substitution urethroplasty. Urology 2011;78(3 Suppl):S118-9.
24. State University of New York - Upstate Medical University. Liquid buccal mucosa graft urethroplasty [Internet]. Bethesda (MD): U.S. National Library of Medicine; c2017 [cited 2019 Dec 15]. Available from: https://ClinicalTrials.gov/show/NCT03061344.
25. Wharton IP, Anderson PCB. Buccal mucosal graft harvest for urethroplasty: closure or nonclosure of the donor site? Eur Urol Suppl 2010;9:144.
26. Oslo University Hospital, Sahlgrenska University Hospital, Region Örebro County, Helsinki University Central Hospital. Scandinavian urethroplasty study [Internet]. Bethesda (MD): U.S. National Library of Medicine; c2020 [cited 2019 Dec 15]. Available from: https://ClinicalTrials.gov/show/NCT02321670.
27. Rourke K, McKinny S, St Martin B. Effect of wound closure on buccal mucosal graft harvest site morbidity: results of a randomized prospective trial. Urology 2012;79:443-7.
28. Wong E, Fernando A, Alhasso A, Stewart L. Does closure of the buccal mucosal graft bed matter? Results from a randomized controlled trial. Urology 2014;84:1223-7.
29. Soave A, Dahlem R, Pinnschmidt HO, Rink M, Langetepe J, Engel O, et al. Substitution urethroplasty with closure versus nonclosure of the buccal mucosa graft harvest site: a randomized controlled trial with a detailed analysis of oral pain and morbidity. Eur Urol 2018;73:910-22.
30. Gulani A, Yadav SS, Tomar V, Priyadarshi S, Singh VK. The effect of closure versus nonclosure of lingual mucosa graft harvest site on postoperative morbidity in augmentation urethroplasty: a comparative study. Urol Ann 2019;11:265-9.
31. Muruganandam K, Dubey D, Gulia AK, Mandhani A, Srivastava A, Kapoor R, et al. Closure versus nonclosure of buccal mucosal graft harvest site: a prospective randomized study on post operative morbidity. Indian J Urol 2009;25:72-5.
32. Chua ME, Silangcruz JMA, Ming JM, Sarino EM, DeLong J, Virasoro R, et al. Nonclosure versus closure of buccal mucosal graft harvest site: a systematic review and meta-analysis of patient-reported outcomes. Urology 2019;125:213-21.

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APPENDIX.

Secondary analysis all eligible trials with relevant outcomes

1. Oral pain

1) Postoperative day #1

Based on four randomized trials reporting this outcome [27-29,31] the evidence is very uncertain about the effect of non-closure of the buccal/lingual mucosa graft harvest site on oral pain compared to closure (SMD: -0.37, 95% CI: -0.75 to 0.01, I^2=51%, very low certainty evidence; Table 2, Supplement Fig. 10). We downgraded the evidence certainty for risk of bias, inconsistency and imprecisiodP n. Subgroup analysis stratified by graft closure technique showed that the test for interaction was not significant (p=0.87, I^2=0%; Supplement Fig. 10).

2) Postoperative day #3 to 6

Based on five randomized trials reporting this outcome [27-31], the evidence is very uncertain about the effect of non-closure of the buccal/lingual mucosa graft harvest site on oral pain compared to closure (SMD: 0.08, 95% CI: -0.3 to 0.47, I^2=61%, very low certainty evidence; Table 2, Supplement Fig. 11). We downgraded the evidence certainty for risk of bias, inconsistency, and imprecision. Subgroup analysis stratified by graft closure technique showed that the test for interaction was not significant (p=0.26, I^2=21.4%; Supplement Fig. 11).

2. Oral numbness

Based on four studies [27,29-31] with 6 months follow up, the evidence is very uncertain about the effect of non-closure of the buccal/lingual mucosa graft harvest site on oral numbness compared to closure (RR: 0.86, 95% CI: 0.42 to 1.77, I^2=55%, very low certainty evidence; Table 2, Supplement Fig. 12). We downgraded the evidence certainty for risk of bias, inconsistency, and imprecision.

3. Salivary problems

Based on two studies [29,31] on postoperative day 1, the evidence is very uncertain about the effect of non-closure of the buccal/lingual mucosa graft harvest site on salivary problems compared to closure (RR: 0.65, 95% CI: 0.11 to 3.96, I^2=50%, very low certainty evidence; Table 2, Supplement Fig. 13). We downgraded the evidence certainty for risk of bias, inconsistency, and imprecision.

4. Delayed oral intake

1) Postoperative day #1

Based on three studies [27,29,31], the evidence is very uncertain about the effect of non-closure of the buccal/lingual mucosa graft harvest site on delayed oral intake compared to closure (RR: 0.61, 95% CI: 0.20 to 1.92, I^2=87%, very low certainty evidence; Table 2, Supplement Fig. 14). We downgraded the evidence certainty for risk of bias, inconsistency and imprecision.

2) Postoperative day #3 to 6

Based on four studies [27,29-31], the evidence is very uncertain about the effect of non-closure of the buccal/lingual mucosa graft harvest site on delayed oral intake compared to closure (RR: 0.66, 95% CI: 0.31 to 1.39, I^2=57%, very low certainty evidence; Table 2, Supplement Fig. 15). We downgraded the evidence certainty for risk of bias, imprecision and inconsistency.