



# Closure versus Non-closure Buccal Mucosal Graft Site for Lowering Post-operative Morbidity in Patient with Urethral Stricture Underwent Urethroplasty: A Systematic Review and Meta-analysis

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## Abstract

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**BACKGROUND:** Buccal mucosal graft (BMG) has been a widely known technique for anterior urethral reconstruction; however, the studies regarding its morbidity are still limited.

**AIM:** The purpose of this study is to compare postoperative morbidity outcome between closure versus non-closure BMG harvest site in patients with urethral stricture underwent urethroplasty.

**METHODS:** A systematic review and meta-analysis of randomized controlled trials and prospective cohort studies was conducted. Literature searching was done through electronic databases, including PubMed, Science Direct, EBSCO, ProQuest, and Google Scholar. The inclusion criteria were men diagnosed with urethral stricture and underwent urethroplasty procedure. The participants were two groups of patients divided based on whether their BMG harvest site was closed or left open. No exclusion criteria applied to the types of participants. The statistical analysis was performed using Review Manager version 5.3 software. Cochrane risk-of-bias tool was used to evaluate the quality of the study.

**RESULTS:** We analyzed five studies qualitatively and three studies quantitatively. There was no significant difference between the closure and non-closure BMG in pooled standard mean difference (SMD) on the oral pain in day-1 and month-6 post-operation. However, pain score in day-1 post-operation was slightly higher in the closure group (SMD 0.49, 95% CI -0.31, 1.30). The incidence of perioral numbness in day-1 post-operation was significantly higher in the closure group (RR 1.48, 95% CI 1.04, 2.10,  $p < 0.05$ ). The incidence of difficulty in opening mouth in day-1 post-operation also significantly higher in closure group (RR 1.48, 95% CI 1.14, 1.91,  $p = 0.003$ ). There was no significant morbidity difference between two groups reported in five studies included after 6 months post-operation.

**CONCLUSION:** There was no significant difference between closure and non-closure of BMG in the post-operative pain morbidity. However, the incidence of the early perioral numbness and difficulty in mouth opening was significantly lower in non-closure group.

## Introduction

In 1992, Burger *et al.* first preliminary described the use of buccal mucosal graft (BMG) for reconstruction of anterior urethra. Not only has acceptable postoperative outcomes, BMG which mainly harvested from inner cheeks or lower lip also has minimal morbidity. However, there are only few studies with small number of patients, which report about the oral complications [1].

There are relatively sparse reports and different opinions on donor site morbidity. There is also ongoing debate of whether closure versus non-closure of buccal mucosal donor site affects this. To date, we are aware of one prospective study [2] and three randomized controlled trials (RCTs) [1], [3], [4], [5] which have found that non-closure leads to less pain and earlier return to diet. Meanwhile, we found one RCT that shown less pain in closure group [4].

At present, there are no systematic review and meta-analysis published comparing the post-operative

morbidity of closure and non-closure BMG used in urethroplasty. We hope that by conducting this review and analysis, definite conclusion regarding the lower morbidity between the two techniques could be achieved. Thus, clinicians could decide whether to use closure or non-closure BMG.

## Methods

A literature search was conducted on November 18, 2019 in several electronic databases, including PubMed, Science Direct, EBSCO, ProQuest, and Google Scholar (Figure 1). The keywords used were (urethral stricture) AND (urethroplasty) AND (closure) AND (non-closure) AND (buccal mucosa\* graft OR oral mucosa\* graft). The literature search was not limited by date of publication but restricted to articles published in English only.

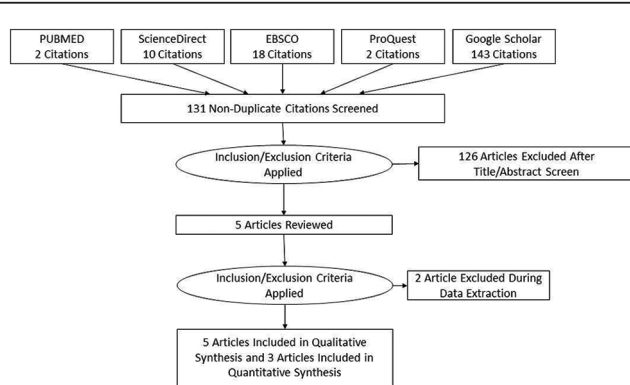


Figure 1: Study flow diagram

## Criteria for studies

### Types of studies

This systematic review and meta-analysis used RCTs and prospective cohort studies about closure compared with non-closure BMG in patient underwent urethroplasty. Only full-text, English-language, and published studies were included in the review. Studies that classified as “case report,” “review article,” “systematic review,” and “meta-analysis” were excluded in this study.

### Types of participants

The participants were men who diagnosed with urethral stricture and underwent urethroplasty procedure. The participants were two groups of patients divided based on whether their BMG harvest site was closed or left open. No exclusion criteria applied to the types of participants.

### Types of interventions

The intervention was closure compared with non-closure of BMG site in patient with urethral stricture which underwent urethroplasty.

### Types of outcome measures

The primary outcome in the present study was the oral pain score that reported by the patient on post-procedure at day-1 and after 6 months. Pain score was assessed with visual analog scale (VAS) or Numeric Pain Scale. Secondary outcomes in this study were perioral numbness and difficulty in opening mouth, salivatory problems, and retention cysts.

## Study selection and data collection

All studies that were obtained from the databases were assessed manually for duplication. Two authors were independently selected the studies based on inclusion and exclusion criteria. Difference between

the two authors was solved by discussion. Studies that met the requirements underwent full-text review.

## Evaluation of biases and statistical analysis

The Cochrane risk of bias assessment tools were used in the present study. Two authors were independently conducted the evaluation. The statistical analysis was performed using Review Manager version 5.3 software. The size effects measured using mean difference for the primary outcome and risk ratio for the secondary outcomes. The heterogeneity was assessed by calculating the  $I^2$  and interpreted into low (25–50%), moderate (50–75%), and high (>75%).

## Results

### Study selection

The authors have identified 131 relevant literatures from literature searching. After thoroughly screening their titles and abstracts, 126 articles were excluded from the study. Therefore, five articles were reviewed as reference to determine literatures that fulfill the inclusion criteria of the study. The final results of literature searching identified five relevant literatures will be reviewed qualitatively and three relevant literatures will be reviewed quantitatively in this study (Figure 1).

### Participants and intervention

Based on five relevant literatures, sample number obtained are 309 patients who underwent urethroplasty. Total patients who underwent urethroplasty with closure BMG was as many as 150 patients, while non-closure one was 159. Meanwhile, the sample number included in the quantitative measurement are 134 patients divided into 67 patients with closure BMG and 67 patients with non-closure BMG. The study sample ages ranged from 17 to 73 years old.

### Comparison

All of the three relevant literatures are analyzed post-operative pain in day-1, while the post-operative pain in month-6 only analyzed two studies. Meanwhile, the secondary outcomes which are the incidence of perioral numbness and difficulty in opening mouth generated from two studies.

### Outcome

We assessed several outcomes identified within studies by questionnaire. They are oral pain

using VAS, perioral numbness, as well as difficulty in opening mouth. Both perioral numbness and difficulty in opening mouth were assessed by how many patients experienced such symptoms. Then, oral pain was analyzed by calculating its standard mean difference (SMD), while perioral numbness and difficulty in opening mouth were analyzed by calculating its risk ratio. Other outcomes that were not quantitatively analyzed were salivatory problems and the incidence of retention cysts.

Oral pain scale was analyzed in day-1 and month-6 post-operation (Figure 2). In the day-1, the pain scale was not significantly different with the SMD of 0.49 [-0.31, 1.30]. However, these three trials had high heterogeneity ( $\text{Chi}^2 = 10.37$ ;  $p = 0.006$ ;  $I^2 = 81\%$ ). The possible cause of this high heterogeneity was the dissimilarity of the baseline characteristic between two groups. In the month-6, the pain scale was also not significantly different with the SMD  $-0.01$  [-0.44, 0.42]. The heterogeneity inter-studies degree was low ( $\text{Chi}^2 = 0.00$ ;  $p = 0.95$ ;  $I^2 = 0\%$ ).

Within this study, perioral numbness was assessed in day-1, after 1 week, and after 6 months post-operation, as shown in Figure 3. In day-1, the incidence of perioral numbness was statistically significant higher in closure group (RR = 1.48, 95% CI 1.04–2.10,  $p < 0.05$ ). There were no statistically significant difference between two groups for perioral numbness both at 1 week (RR 1.63, 95% CI 0.98–2.71) and 6 months post-operation (RR = 1.87 95% CI 0.87–4.03). The  $I^2$  heterogeneity tests were applied for these studies reviewed the incidence of perioral numbness and get 0% either at day-1, after 1 week, or after 1 months and get 0%. Forest plots for perioral numbness look symmetrical collected.

The incidence of difficulty in opening mouth at day-1 was statistically significant higher in closure group

(RR 1.48, 95% CI 1.14–1.91,  $p = 0.003$ ). However, there were no statistically significant at 1 week (RR 1.30, 95% CI 0.74–2.27) and 6 months (RR 0.74, 95% CI 0.19–2.87) post-operation (Figure 4).

Regarding qualitative analysis, there are three studies comparing salivatory problem, but they used different assessment [1], [3], [5]. Muruganandam *et al.* [1] reported that three patients had salivatory problems on ipsilateral side and in closure group, while none of these problems experienced in non-closure group. However, this difference was not statistically significant. Rourke *et al.* [3] and Soave *et al.* [5] reported as well that there was no statistically significant difference between two groups of closure and non-closure in salivatory problems. Moreover, those three studies revealed that salivatory problems of the patients got better over time [1], [3], [5].

Only one study from five studies compared the incidence of retention cysts between closure and non-closure group. Muruganandam *et al.* reported that only one patient experienced retention cyst in closure group. However, same as salivatory problem, the result was not statistically significant and the problem of the incidence of retention cyst got resolved within 6 months [1].

**Risk of bias assessment**

Based on Cochrane risk of bias assessment, the quality of the studies included in this study was categorized into low-to-moderate risk of bias. However, performance and detection bias were high risk of bias due to difficulty to blind either the patients or the surgeons. The risk of bias assessment is summarized in Figure 5.

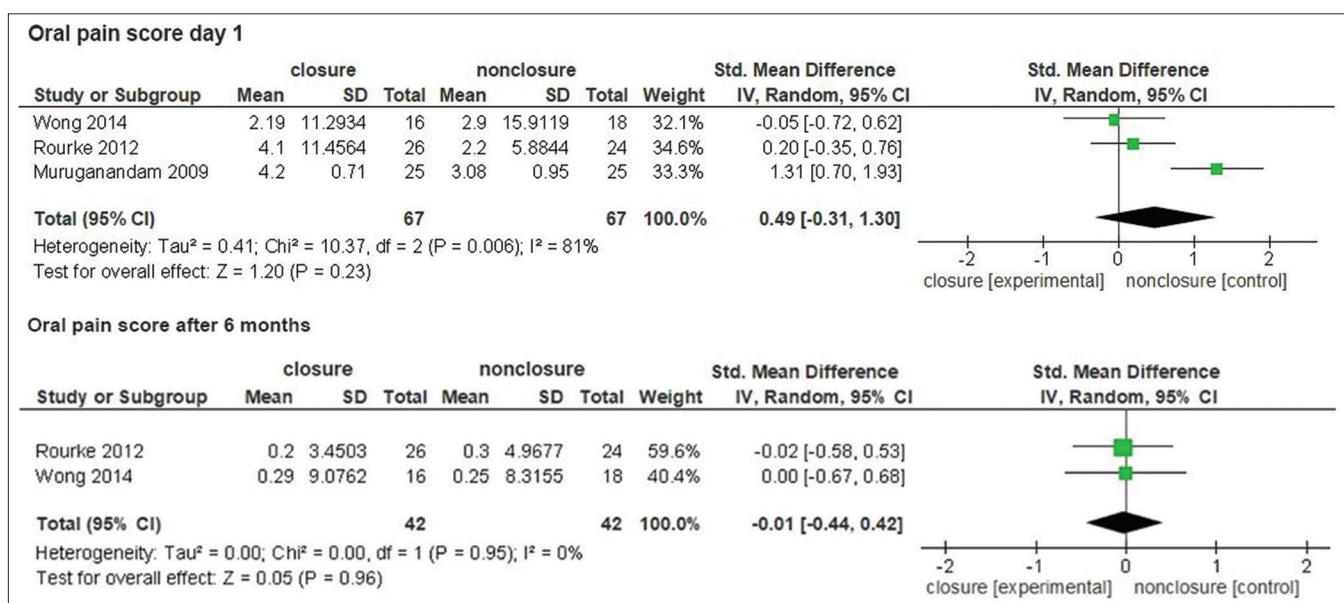


Figure 2: Forest plot oral pain scale in closure versus non-closure BMG in day-1 and month-6 post procedural

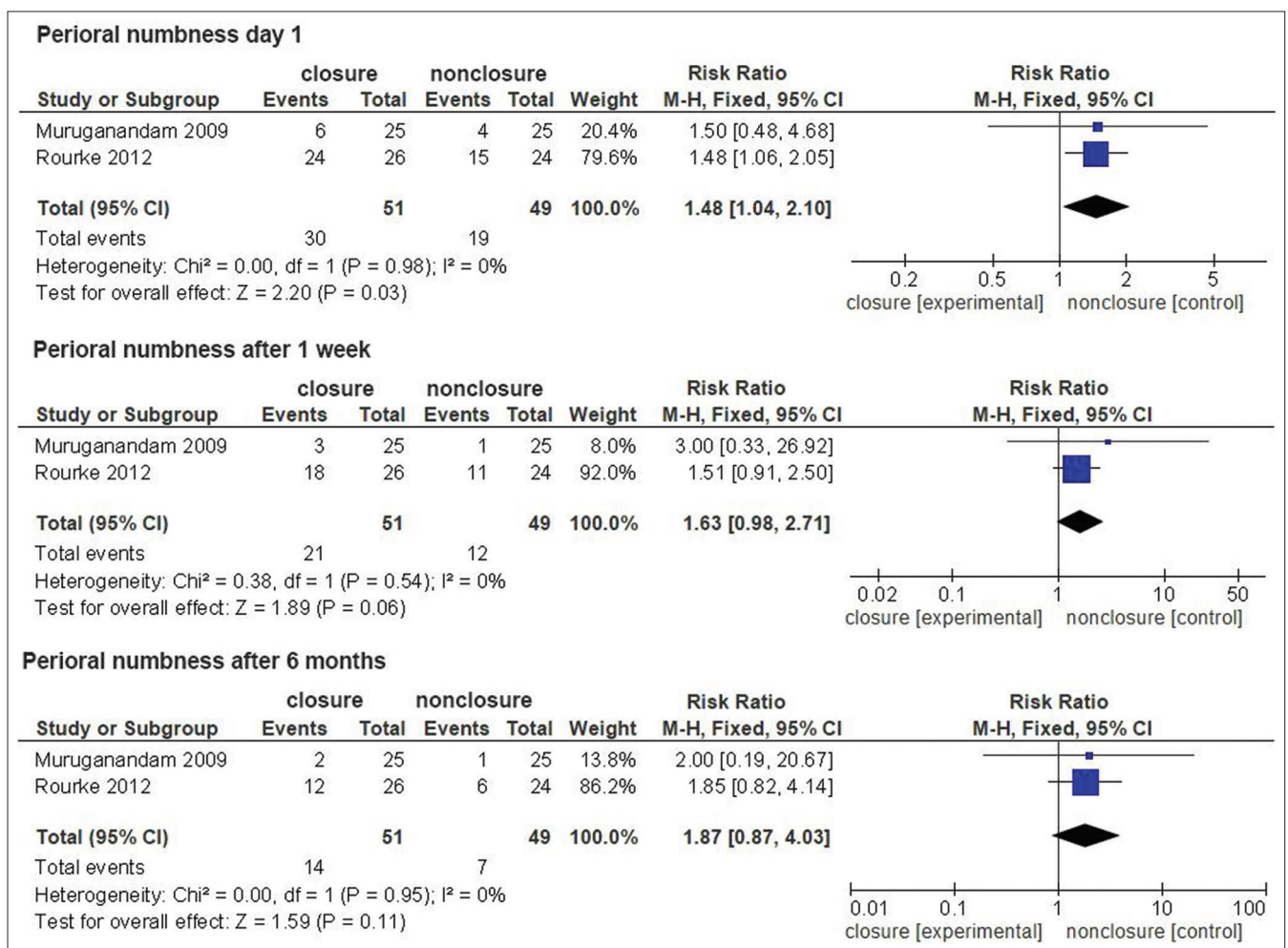


Figure 3: Forest plot of the incidence of perioral numbness in closure versus non-closure BMG in day-1, after 1 week, and after 6 months post procedural

## Discussion

The stricture of urethra is a medical condition, where the urethra narrows due to scar tissue which leads to obstructive voiding dysfunction with considerable consequences for the entire urinary tract [6], [7]. The most common etiology of urethral stricture is iatrogenic (45%) which can be generated from urethral procedure including transurethral intervention. Other etiology of urethral stricture is traumatic urethral rupture due to pelvic fracture. Infection such as bacterial urethritis can also cause urethral stricture. Patients with urethral stricture generally come with obstructive and irritative symptoms, for instance, increased urination time, sensation of incomplete bladder emptying as well as increased frequency and urgency of voiding [6], [7], [8]. Urethral stricture can be diagnosed by taking patient history, performing physical examination, along with several examination such as uroflowmetry, cystourethrography, urethroscopy, or ultrasonography [6], [8]. The treatment options of urethral stricture are endoscopic and open surgical procedures. Endoscopic option is minimally invasive procedure done by bougienage or internal urethrotomy,

whereas open surgical procedure comprises stricture resection and end-to-end anastomosis, urethroplasty with free graft, urethroplasty with pedicled flap, perineal urethrostomy, and bulboprostatic anastomosis [6]. Graft urethroplasty has been commonly used to treat bulbar strictures and all penile strictures. The graft can be harvested from other parts of the body, such as foreskin, oral mucosa, and upper high or lower abdomen [6]. To date, there are two options in graft site's management, whether suturing it (closure) or leaving it open (non-closure) [1], [2], [3], [4], [5].

In this study, we found that oral pain in the BMG area after urethroplasty is not significantly different between closure and non-closure group either in day-1 or month-6 after urethroplasty procedure. However, the pooled SMD in day-1 is as high as 0.49 (−0.31, 1.30). It showed that non-closure of the BMG reduces the oral pain scale although not significant. Whereas at 6 months post-operation, the value of the pooled SMD is as low as −0.01 (−0.44, 0.42). Two studies [2], [5] that not included in the meta-analysis showed that leaving the BMG open reduce the oral pain. In the study by Rourke *et al.* 2012 [3], early postoperative oral pain was decreased in the non-closure BMG. Oral pain can be worse immediately after suturing the harvest site [1].

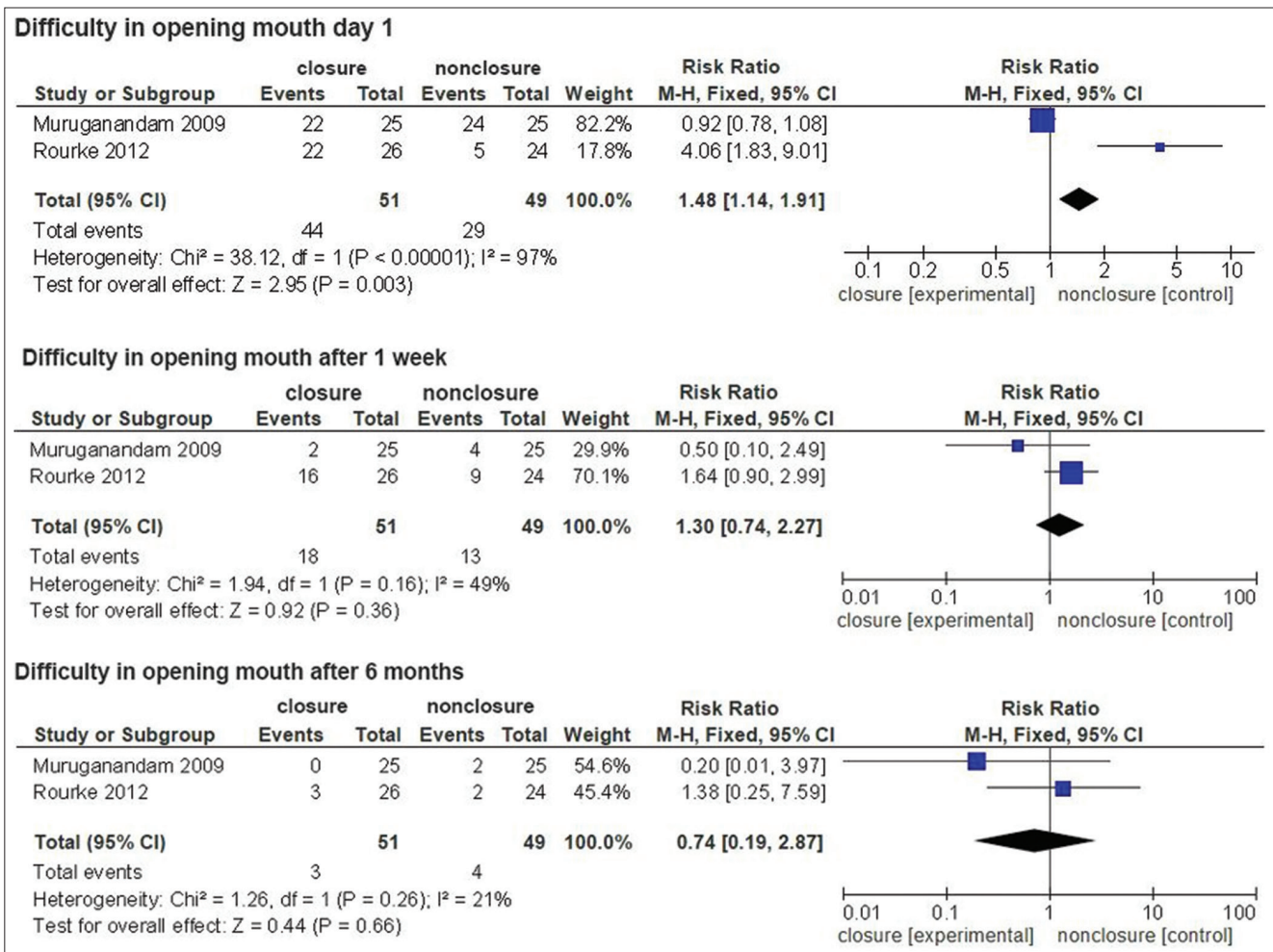


Figure 4: Forest plot of the incidence of difficulty in opening mouth between closure versus non-closure BMG in day-1, after 1 week, and after 6 months post procedural

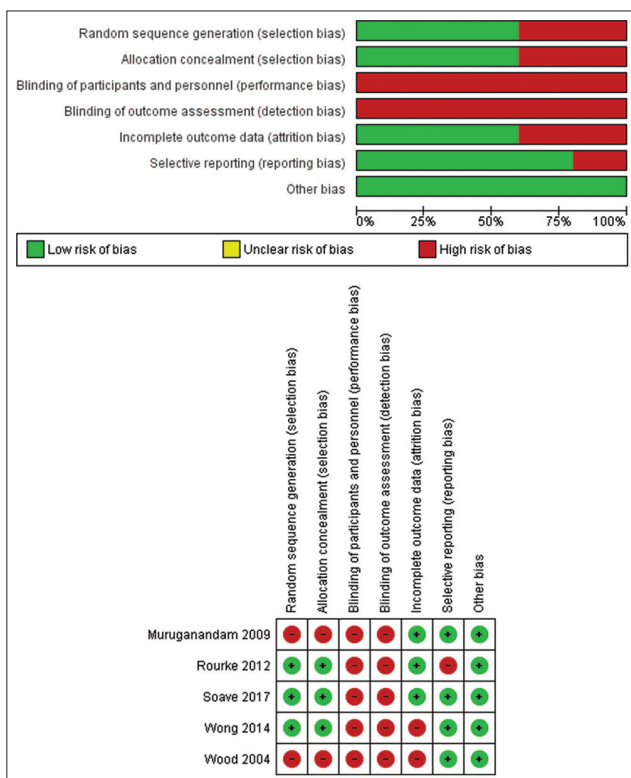


Figure 5: Risk of bias assessment for the included studies

Only one study out of five studies by Wong 2014 that showed closure of the buccal mucosa graft improves pain in the early postoperative period.[4]Muruganandam *et al.* [1] stated that higher pain morbidity may be due to suturing management [1]. Alternative choices for urethroplasty are including injectable antifibrotic agents, lingual grafts, genital and extragenital skin, bladder mucosa, colonic mucosa, and acellular matrix/ tissue engineering. Injectable antifibrotic agents are a less invasive options which also offer high effectivity in selected patients. Complications of lingual graft also causes oral pain with limited for 1–2 days and pain-free after 6 days of procedure. Successful rate of lingual grafts are higher than buccal graft which lead it to be a high quality alternative graft especially in long defects or recurrent stricture [9], [10].

The incidence of early perioral numbness as well as early difficulty in opening mouth within this study is statistically significant lower in non-closure group. However, after 1 week and 6 months, this incidence is not statistically significant different between two groups. From this study, all outcomes identified showed that after 1 week and 6 months post-operation, there was no single morbidity that significantly different between two groups. It was discovered that their morbidity decreased

along with the longer the time after they were out of surgery. In a prospective study by Hölzle *et al.* [11] that involved 15 male participants divided into two groups, the postoperative morbidity was noticeable during its first 3 weeks but after 3 weeks post-operation, oral pain of all patients had resolved. This study supports our findings. However, a retrospective study by Wharton and Anderson [12] involving 88 patients underwent urethroplasty in the United Kingdom, they found that although non-closure group had more pain in the initial post-operative period, these donor sites that were closed heal significantly faster than these which left open.

The strengths of this study are its thorough literature searching and detailed meta-analysis of particular outcomes between closure and non-closure BMG harvest site for urethroplasty. Nevertheless, there were only few RCTs studied the difference between two techniques as well as their small number of patients. Moreover, studies included in this systematic review had different method of assessment and different time of follow-up. Lack of detailed data also found. It is totally recommended to further conduct more comprehensive study comparing closure and non-closure BMG with greater number of samples.

In conclusion, there was no statistically significant difference of postoperative pain morbidity between closure versus non-closure BMG harvest site even though four out of five studies reported that non-closure one gave lesser pain morbidity. However, our meta-analysis suggested that the incidence of early perioral numbness and difficulty in mouth opening was statistically significant lower in non-closure group. Both closure and non-closure groups had no statistically significant morbidity after 6 months post-operation.

## Ethics Approval and Consent to Participate

Not applicable.

## Authors' Contributions

All authors designed the model and the computational framework and analyzed the data, carried out the implementation, performed the calculations, wrote the manuscript with input from all authors, and conceived the study and were in charge of overall direction and planning.

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