SYSTEMATIC REVIEW

OUTCOMES OF RECONSTRUCTION WITH VASCULARIZED VS NON-VASCULARIZED BONE GRAFT AFTER RESECTION OF BONE TUMOURS- A SYSTEMATIC REVIEW AND META-ANALYSIS

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Background: Vascularized (VBG) and non-vascularized (NVBG) bone grafting are two crucial biological reconstructive techniques in the management of bone tumours. The objective of this study is to compare the outcomes of reconstruction with vascularized and non-vascularized bone grafts after resection of bone tumours. **Methods:** A systematic evaluation of the literature from 2012-2021 was undertaken using the online databases PubMed/Medline, Google Scholar, and Cochrane Library considering only comparative articles with specific outcomes for the restoration of the defect with vascularized and non-vascularized bone graft following the resection of bone tumours. The quality of the research methodology was evaluated using Oxford Quality Scoring System and Newcastle Ottawa Scale for randomized trials and non-randomized comparison research respectively. The SPSS version 23 was used to examine the data that was collected. Musculoskeletal tumour society score (MSTS), bone union time, and complications were the outcomes of this review. **Results:** Four clinical publications were considered, totalling 178 participants (92 men and 86 women) with 90 patients with VBG and 88 with NVBG. MSTS score and bone union time were the key outcomes that were measured. The overall MSTS (p>0.05) and rate of complications (p>0.05) results were comparable between the two groups, however, VBG had a better rate of bone union (p<0.001). **Conclusion:** As a result of the quicker bone union, our systematic evaluation demonstrated that VBG causes earlier recovery. Complication rates and functional results were the same in both groups. The link between the bone union time and functional score following VBG and NVBG must also be demonstrated.

Keywords: Reconstruction techniques; Vascularized bone grafting; Non-vascularized bone grafting; Bone tumour; Resection

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INTRODUCTION

Primary bone tumour originates in bone cells. It is a rare tumour type compared to metastatic bone tumours. An estimated annual incidence rate of 0.8 cases per 100,000 individuals of bone tumours represents a rare tumour entity.[1] The three main types of malignant bone tumours are osteosarcoma, Ewing's sarcoma, and chondrosarcoma whereas the most common benign tumours of bone are osteochondromas and giant cell tumours.[2,3]The familiar symptoms of these tumours are pain, swelling and deformity.[4] Resection and reconstruction is the preferred approach for most bone tumours.[5] Reconstructive procedures have been accomplished comprising of the prosthesis, vascularized bone grafts (VBG), and non-vascularized bone grafts (NVBG).[6] Bone grafting is a method where the bone defect is reconstructed by using autograft or allograft.[7] It is a widely used procedure for the management of bone deformities and bone loss. Vascularized bone grafting involves the reconstruction of a bone with its vascular supply. It provides blood supply to the bone through the anastomosis of the vascular pedicle.[8,9] Conversely, NVBG has an absence of blood supply in the bone graft and the bone graft depends upon the nourishment from neighbouring bone cells and the medullary cavity.

In recent years, certain systematic reviews were reported. Allsopp *et al.*[10] reported the review where they tried to find out the utility for more than 6 cm of bone defect only and did not focus on VBG and NVBG holistically. Other systematic reviews by Landau *et al.*[11] have shown the utility of VBG, but they did not include a comparative approach between VBG and NVBG. Othman *et al.*[12] and Houben *et al.*[13] have compared the utility of VBG with NVBG but focused on the lower limb only. Therefore, we were

not able to find reviews where VBGs and NVBGs are compared after tumour resection and reconstruction surgery to establish clinical guidance.

The main goal of our research was to study the functional outcomes of vascularized and non-vascularized bone grafts after tumour resection. The aim was to investigate the functional restoration, bone union time and the complications that occurred between VBGs and NVBGs. Our study was performed to make a comparative approach between VBG and NBG.

MATERIAL AND METHODS

The "Preferred reporting items for systematic reviews and meta-analysis (PRISMA)" tool was used to collect data on the results after the reconstruction of vascularized and non-vascularized bone grafts after resection of bone tumours. To guarantee quality assessment ratings, the available literature was examined. The PRISMA chart is shown in figure-1.

The PubMed/Medline, Google Scholar and Cochrane Library were searched methodologically from 2012 to 2021 with the MESH terms "vascularized bone graft", "non-vascularized bone graft", "bone tumours" and "reconstruction" using various combinations for comparative trials in English on the human specimen. The references of trials that were included were also examined for relevant studies.

The inclusion and exclusion criteria were decided upon following discussions among the authors. Only comparative studies, such as randomized trials and cohort studies with specific outcomes for the restoration of the defect with vascularized and non-vascularized bone grafts following the resection of bone tumours, were taken into consideration. Trial participants were not allowed to undergo any other prior reconstruction. Participants who underwent bone graft surgery to repair a fracture were also eliminated. Complete surgical resection or curettage was the only therapy allowed, together with or without pharmaceutical treatment like denosumab, bisphosphonates, or steroids. However, radiotherapy of adjuvant or neoadjuvant was used in the trials. Other exclusions from the study were letters, brief communications, commentaries, editorials, case reports, cohort studies, cross-sectional studies, conference papers, proceedings, and personal communications. The corresponding author of this article contacted the trial authors to inquire about any other outcomes that might have occurred in their study prior to exclusion, in the event of no response or an unwanted response.

Three authors (S. M. E. A., D.C., U.R.A.) independently evaluated the research's methodological quality using the "Oxford quality scoring system (OQSS)" for randomized trials. According to the Oxford quality scoring system, a score of 5 or 4 denotes a high-quality trial, a score of 3 or 2 denotes an average trial, and a score of 1 or 0 denotes a low-quality study.[14] Modified Newcastle-Ottawa Scale was used for non-randomized comparison research; above 7 stars indicate an excellent trial, 4–7 stars indicate a fair trial and less than 4 stars indicate a poor trial.[15] Internal discussions among the writers were used to resolve any differences. If issues did not get resolved after conversations, an expert was brought in table-1 shows the estimated biased risk.

The following data was taken from each study by the three authors (S.K., S.W.F., S.K, and B.S.), i.e., year of publication, country of the study, study design, population size, participants in each group, surgical intervention, gender, age, follow-ups, MSTS, duration of union, and complications. The extracted data is displayed in tables 1 and 2.

The major outcomes of this systematic review are the functional outcome measured by the musculoskeletal tumour society score (MSTS) and the time to union, whereas the secondary outcomes include the frequency of complications including infections, fractures, non-union, and reoperations (Table-3).

It took two authors to create the data analysis (S.M.E.A., B.S, and S.W.F.). The authors (S.M.E.A., S.K., and D.K.) used SPSS, version 23 to analyze the data (IBM Corp, Armonk, New York). The categorical variables were expressed as numbers while the continuous variables were expressed using the Mean +_standard deviation. In the forest plots, the estimate was grouped using the risk ratio (RR), which had a 95% (95% CI) confidence interval. The categorical data were plotted in a 2×2 table. The results were plotted using the DerSimonian and Laird random-effects, generic inverse variance approach in the OpenMetaAnalyst Software. The RR of complications and re-operations after VBG and NVBG were combined using a random-effects model with a 95% confidence interval (95% CI), whereas the estimates for the MSTS and length of the union after VBG and NVBG were combined using the standardized mean difference (SMD). I2. Statistics assessed the heterogeneity. The heterogeneity was considered negligible when there was an I^2 of less than 25%; low when there was an I^2 of 26–50%; moderate when there was an I^2 of 51–75%; high, when there was an I^2 above 75%. To predict the factors influencing the success and failure of the VBG and NVBG, the random-effect meta-regression was used to examine the significantly moderate or high between-study heterogeneity (I^2 >50%, *p*-0.05) for primary outcomes. If ten or more papers are determined to be appropriate for inclusion, the publication bias will be evaluated using the funnel plot and Egger's and Begg's tests.

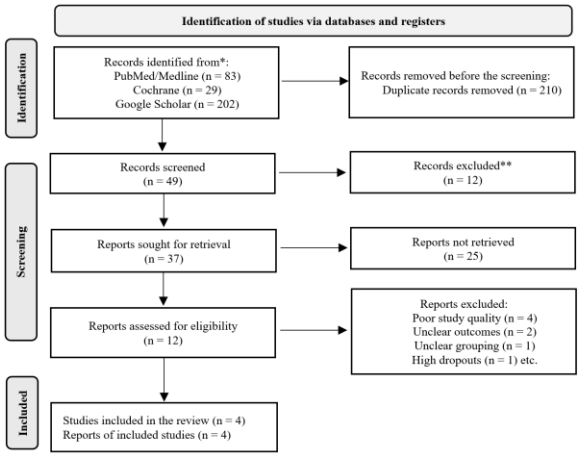

Figure-1: PRISMA chart showing the inclusion and exclusion of studies

RESULTS

During the search for literature from databases, we identified 83 studies from PubMed/Medline, 29 studies from Cochrane and 202 studies from Google Scholar. The studies were screened by titles and 210 duplicate studies were removed. During the abstract screening of 49 articles after duplicate removal, 37 articles were excluded, while full texts of 12 studies were reviewed for eligibility according to the inclusion and exclusion criteria. eight studies were excluded after reading the full text due to ineligibility, poor methodology, unclear outcomes, high rate of dropouts and ambiguous grouping.

Four studies, comprising 90 patients with VBG and 88 NVBG, totalling 178 subjects with 92 males and 86 females, were included in this review, as shown in Table I. The studies were based in Austria (n= 1), the USA (n= 2), and Canada (n=1). Two studies were of good quality and two studies were of fair quality. The means of age and follow-up in months of the candidates in included studies was 22.08±7.95 years and 71.57±17.47 months, respectively.

The primary outcomes of our systematic review focused on the MSTS score among VBG and NVBG groups. The difference in SMD between VBG and NVBG remained insignificant with 0.021 [95% CI= -0.274, 0.316; p>0.05] with statistically insignificant heterogeneity (I^2=0%; p=0.72). Therefore, the functional outcomes were the same between both groups as shown in figure-2.

The other outcome was focused on the incidence of complications among VBG and NVBG groups. The difference in RR between VBG and NVBG remained insignificant with 1.249 [95% CI= -0.608, 2.564; p> 0.05] with statistically insignificant heterogeneity (I^2=50.8%; p=0.107). Hence, the rate of complications is similar as shown in figure-3.

The primary outcomes of our systematic review focused on bone union time among VBG and NVBG groups. The difference in SMD between VBG and NVBG remained insignificant with -0.064 [95% CI= -1.112, 0.984; p> 0.05] with statistically significant heterogeneity (I^2=88.19%; p<0.001) as shown in figure-4. Therefore, the odd one out was attempted to decrease heterogeneity by removing studies one by one.

After the exclusion of Schuh *et al.*[17], the SMD between VBG and NVBG showed that the difference among the group was statistically significant with 0.452 (95% CI= 0.005, 0.899; p< 0.05) as shown in figure-5. The heterogeneity value dropped to 0% (I^2=0%; p= 0.897).

Table-1: Study characteristics of the studies included in the review

Study Name	Year	Country	Study Design	Surgery performed	Total Patient	VBG vs NVBG	Age	Gender M: F	Follow-up	Study Quality
Estrella *et al.*[16]	2017	USA	Comparative study	Fibular grafting	52	25:27	23.8±9.8	25:27	37.5±30.95	Good
Schuh *et al.*[17]	2014	Austria	Comparative study	Diaphyseal resection and reconstruction	53	26:27	20.5±9.52	26:27	53.7±9.17	Good
Clarkson *et al.*[18]	2013	Canada	Comparative study	Wrist arthrodesis with fibular and iliac graft	27	14:13	32.5±10	11:16	NA	Fair
Errani *et al.*[19]	2021	USA	Comparative study	femoral intercalary reconstruction	46	25:21	11.5±2.5	30:16	123.5±12.34	Fair

Table-2: Outcomes of included studies

Study Name	MSTS in VBG	MSTS in NVBG	Complications in VBG	Complications in NVBG	Bone union time in VBG	Bone union time in NVBG
Estrella *et al.*[16]	83.5±10.6	81.8±15.3	3	7	12.8±5.8	10.6±4.2
Schuh *et al.*[17]	77.9±8.25	75.8±15	19	9	6.1±1.05	10±4.88
Clarkson *et al.*[18]	90±12.5	90±15	1	2	6.9±3.3	5.5±2
Errani *et al.*[19]	86.33±11.67	89±7.67	11	6	NA	NA

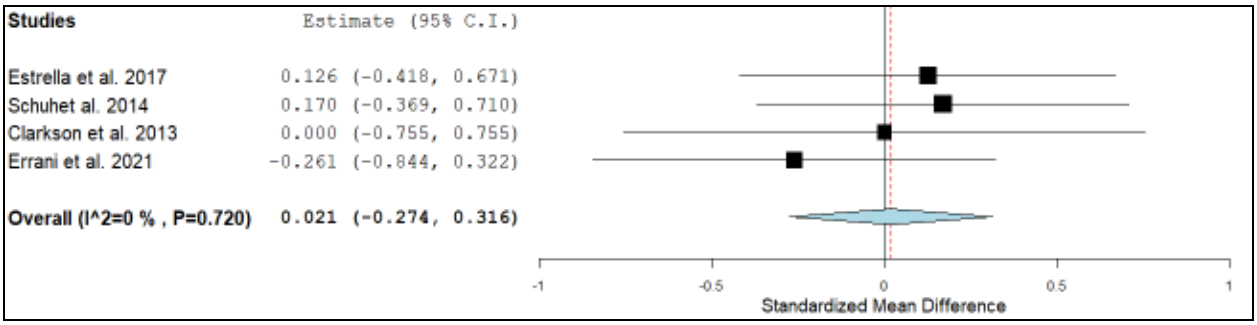

Figure-2: Forest plot showing the standardized mean difference (SMD) estimates for the MSTS after VBG vs. NVBG, in which the boxes show the effect size, with the length of the corresponding line explaining the 95% confidence interval and the diamond-shaped symbol representing the overall effect size.

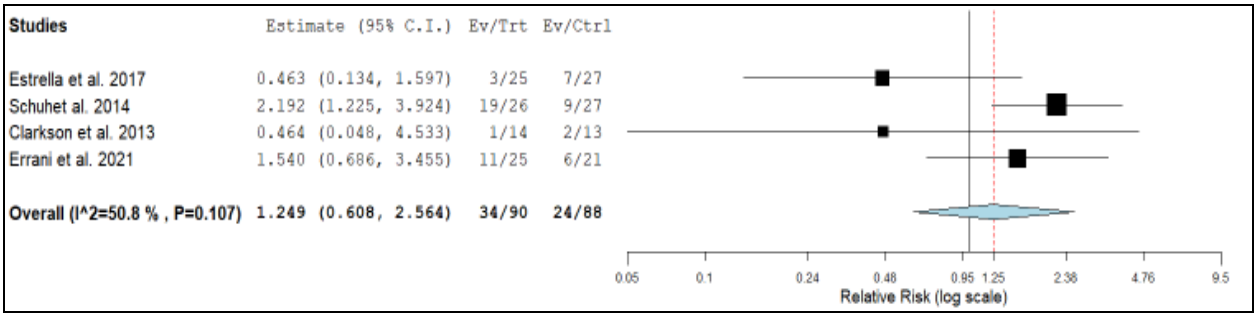

Figure-3: Forest plot showing the risk ratio (RR) estimates for the incidence of complications after VBG vs. NVBG, in which the boxes show the effect size, with the length of the corresponding line explaining the 95% confidence interval and the diamond-shaped symbol representing the overall effect size.

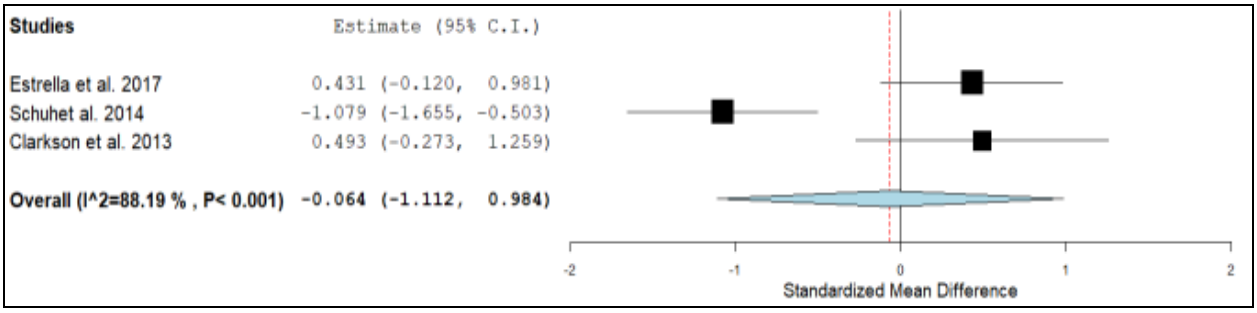

Figure-4: Forest plot showing the standardized mean difference (SMD) estimates for the bone union time after VBG vs. NVBG, in which the boxes show the effect size, with the length of the corresponding line explaining the 95% confidence interval and the diamond-shaped symbol representing the overall effect size.

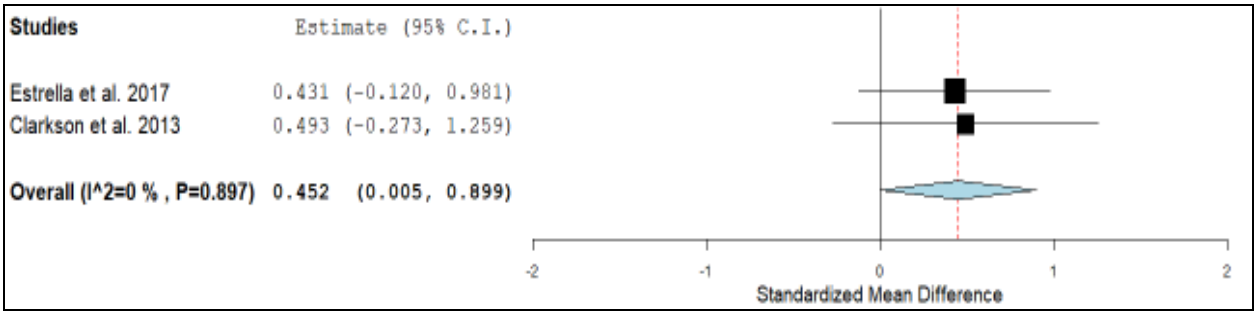

Figure-5: Forest plot showing the standardized mean difference (SMD) estimates for the bone union time after VBG vs. NVBG, in which the boxes show the effect size, with the length of the corresponding line explaining the 95% confidence interval and the diamond-shaped symbol representing the overall effect size.

DISCUSSIONS

Surgical resection has been the most favoured treatment option for bone tumours due to the radioresistant nature and lack of chemotherapeutic penetrance of bone. After resection, reconstruction is conducted by either prosthetic or natural reconstruction. Prosthetic reconstruction may ensure early recovery, but long-term complications are established. Hence, bone grafting has been used extensively to overcome bone defects after pathological or traumatic bone loss. The Iliac crest, proximal part of the tibia, the distal end of the radius, the distal aspect of the tibia, proximal fibula, fibular strut, and greater trochanter remain the favoured site for bone grafting.[20] A debate came to focus regarding the use of vascularized or non-vascularized grafts. We conducted this study to investigate the functional outcomes of VBG and NVBG after resection for bone tumours. Recent systematic reviews of Landau *et al*.[11], Othman *et al*.[12], and Houben *et al*.[13] have shown the utility of VBG but these studies included single-armed studies and did not focus on the comparative aspect of VBG vs NVBG.

From our results, we may consider that the functional outcomes remained the same in both groups. Therefore, the utility of VBG and NVBG remains similar while considering pain, movements, load-carrying abilities, and other social activities. The results have been contrary to the previous systematic reviews.[11,13] However, we have considered a comparative approach where a comparison is set between VBG and NVBG which allowed only two armed studies to be included in the review. Othman *et al*.[12] confirmed that better functional outcomes were achieved within both groups. However, their review focused on the lower extremity only. Another strengthening feature remains the lack of heterogeneity among the studies included after quality appraisal scoring. However, it might be the case where better functional outcomes have been achieved earlier in any of the groups. From our literature review, further studies are needed that focus on achieving better functional outcomes relative to the time among VBG and NVBG groups. Moreover, we did not find studies comparing the biochemistry and physiology of VBG and NVBG.

The bone union time was shown to be better in our review of literature among the VBG group. The results are well supported by Othman *et al*.[12] The time of bone unions depends upon the nourishment supplied to the bone via blood.[21] It has been evident that the macrophages induce bone remodelling that leads to earlier growth spurts and clearance of debris.[22] However, we were not able to find any study that focuses on the relationship between bone union time and functional outcomes. Therefore, VBG remains a better option due to earlier recovery and may be helpful in reducing the need for follow-ups. Most of the primary bone tumours share bimodal age distribution.[3] Therefore, it may be an effective option for younger patients who require early rehabilitation.[23] However, one must keep in mind that VBGs require higher intraoperative duration.[24] Hence, appropriate selection criteria for patients to undergo VBG is required.

The review also presented the idea of complications among VBG and NVBG groups. The rate of complications was statistically similar in both groups. The results of our review are contrary to Allsopp *et al*.[10], Gorski *et al*.[25], and Eward *et al*.[26] where VBGs were considered to have high complication rates. We considered postoperative infections, bone resorption, and graft failures as complications. From the histological perspective, vascularized bone is considered to have better circulation leading to accelerated healing.[27] But Zhang *et al*.[28] and Moran *et al*.[29] establishing higher vascularization lead to easier reperfusion injuries of the tissue with free oxygen radicals. Secondly, from Marenzana *et al*.[30] we know that bones are tolerant to mild ischemic injury and have a better chance of survival with gradual reperfusion. Appropriate selection of patients to undergo VBG may produce lesser complications as previous studies have shown that younger patients have better antioxidation to overcome reperfusion injury.[31]

Our systematic review had certain limitations. Firstly, we had only four studies therefore regression analysis and publication bias tests were not performed due to a lack of statistical feasibility. Secondly, none of the studies in the literature used randomized trial methodology. Thirdly, the study focused on VBG and NVBG only while prosthesis use has been overlooked.

In conclusion, our systematic review showed that VBG produces earlier recovery due to accelerated bone union. The rate of complications and functional outcomes remained the same in both groups. Therefore, further studies are required to conclude VBG or NVBG as the sole successful method of treatment for bone defects in tumours and reconstruction surgery. An approach is also necessary to prove the relationship between bone union time and functional outcomes after VBG and NVBG.

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Conflict of Interest: None

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