COMPARATIVE STUDY OF CLINICAL OUTCOMES OF VASCULARISED VERSUS NON-VASCULARISED FIBULAR GRAFT RECONSTRUCTION AFTER WIDE RESECTION OF GIANT CELL TUMOUR OF DISTAL RADIUS

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Comparative Study Of Clinical Outcomes Of Vascularised Versus Non-Vascularised Fibular Graft Reconstruction After Wide Resection Of Giant Cell Tumour Of Distal Radius

FROM THE YEAR 2000 TO 2019

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AND

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LIST OF ABBREVIATIONS

i.	HUSM	Hospital Universiti Sains Malaysia
ii.	UMMC	University Malaya Medical Centre
iii.	GCT	Giant cell tumour
iv.	VFG	Vascularised fibular graft
v.	NVFG	Non-vascularised fibular graft
vi.	OORU	Orthopaedics Oncology and Reconstructive Unit
vii.	PRS	Plastic and Reconstructive Surgery
viii.	IQR	Inter quartile range
ix.	SD	Standard deviation

ABSTRAK

Pengenalan

Giant cell tumour (GCT) pada tulang radius adalah tumour benign tetapi boleh menjadi agresif. Tumour ini boleh merosakkan tulang dan mungkin mengakibatkan kecacatan sendi. Untuk *Campanacci* gred III dan beberapa gred II biasanya dirawat dengan reseksi luas dan diikuti dengan rekonstruksi semula dengan menggunakan autograf tulang fibula vaskular (VFG) atau tidak vaskular (NVFG) dan kedua-duanya dilaporkan memberi hasil yang baik. Kami ingin membandingkan hasil klinikal kedua-dua kumpulan rawatan ini.

Kaedah Kajian

Ini adalah kajian keratan rentas pelbagai pusat yang melibatkan Hospital Universiti Sains Malaysia (HUSM) dan Pusat Perubatan Universiti Malaya (UMMC). Pesakit yang didiagnosis dengan GCT radius dan menjalani reseksi luas diikuti dengan rekonstruksi semula dengan VFG atau NVFG antara tahun 2000 dan 2019 di pusat masing-masing dengan minimum 1 tahun rawatan susulan. Indikasi untuk VFG adalah *Campanacci* gred III, perebakan tisu lembut yang banyak, ketumbuhan yang besar, dan kepatahan tulang. Seramai 21 pesakit (7 VFG dan 14 NVFG) yang memenuhi kriteria berumur median 27 tahun telah dipanggil untuk penilaian menggunakan skor "musculoskeletal tumour society" (MSTS). Di antara 21 pesakit, 9 adalah lelaki (5 VFG, 4 NVFG) dan 12 adalah wanita (2 VFG, 10 NVFG). Percantuman tulang ditentukan oleh radiografi dengan kalus sekurang-kurangnya tiga korteks dalam dua pandangan. Ujian *Mann-Whitney U bukan parametrik* digunakan untuk analisis statistik dengan SPSS versi 24.

Keputusan

Keseluruhan skor MSTS, NVFG adalah 80%, lebih baik daripada VFG iaitu 73.3%, tetapi secara statistik tidak signifikan dengan nilai-p 0.60. Sebagai perbandingan setiap komponen dalam skor MSTS didapati tiada perbezaan yang signifikan dalam kesakitan (p = 0.48), fungsi (p = 0.94), emosi (p = 0.50), kedudukan tangan (p = 0.61), ketangkasan manual (p = 0.93) dan keupayaan mengangkat (p = 0.89). Perbezaan rata-rata kadar percantuman untuk VFG adalah 30 minggu (IQR = 31) sementara kumpulan bukan vaskular 22.8 minggu (IQR = 23). Tiada perbezaan yang signifikan dalam kadar percantuman tulang (p = 0.52) di antara kedua-dua kumpulan pesakit ini. Walau bagaimanapun, tulang dua pesakit dari kumpulan NVFG didapati gagal bercantum sedangkan semua pesakit dalam kumpulan VFG mencapai percantuman. Tidak ada morbiditi serius yang dilaporkan dari kedua-dua kumpulan.

Kesimpulan

Secara amnya, pesakit VFG mempunyai tumor yang lebih besar dan melibatkan pembedahan yang rumit. Namun, hasil klinikal adalah sebanding dengan NVFG. VFG mempunyai kadar komplikasi yang lebih tinggi, tetapi ia adalah komplikasi ringan, sedangkan NVFG mempunyai komplikasi serius seperti kegagalan tulang untuk bercantum, penyerapan tulang dan perlunya pembedahan semula. Walau bagaimanapun, ini adalah kajian retrospektif yang melibatkan bilangan sampel yang terhad. Oleh itu, kajian prospektif diperlukan dengan sampel yang lebih banyak untuk bukti yang lebih kukuh.

Kata Kunci:

Tumor sel giant tulang, graf fibula vaskular, tulang radius

ABSTRACT

Introduction

Giant cell tumour (GCT) of distal radius is a benign tumour but can be locally aggressive. The tumour can be devastating to the bone which may result in severe deformity. For Campanacci grade III and some grade II usually treated by wide local excision followed by reconstruction using either autologous vascularised or non-vascularised fibular graft and both were reported with good results. We would like to compare the clinical outcomes of these two groups of treatment.

Materials and methods

This is a multicentre cross sectional study involving Hospital Universiti Sains Malaysia (HUSM) and University Malaya Medical Centre (UMMC). Patients who diagnosed with distal radius GCT and underwent wide resection followed by reconstruction with either autologous vascularised fibular graft (VFG) or non-vascularised fibular graft (NVFG) between year 2000 and 2019 in respective centres with minimum 1 year of follow up were included. Indications for VFG are Campanacci grade III, extensive soft tissue involvement, large tumour and fracture deformity. A total of 21 patients (7 VFG and 14 NVFG) fulfilled the criteria with a median age of 27 years were called for assessment using musculoskeletal tumour society (MSTS) score. Among the 21 patients, 9 males (5 VFG, 4 NVFG) and 12 females (2 VFG, 10 NVFG). Bony union was determined by plain radiograph with bridging callus at least three cortices in two views. Non-parametric Mann-Whitney U test were used for statistical analysis using SPSS version 24.

Results

The Overall MSTS score of NVFG was 80%, better than VFG 73.3% but statistically was not significant with the p-value of 0.60. In comparison of each component in MSTS scoring found

to be no significant difference in pain (p = 0.48), function (p = 0.94), emotional (p = 0.50), hand positioning (p = 0.61), manual dexterity (p = 0.93) and lifting ability (p = 0.89).

Median difference of union rate for VFG was 30 weeks (IQR = 31) while NVFG was 22.8 weeks (IQR = 23). There was no significant difference in union rate (p = 0.52) between these two groups of patients. However, two patients from NVFG group were reported non-union whereas all patients in VFG group achieved union. No serious morbidity reported at donor site from both groups.

Conclusion

Generally, VFG patients have larger tumour, hence more complicated surgeries. However clinical outcomes are generally similar compared to NVFG. VFG has slightly higher complication rates but they are considered minor whereas NVFG has serious complications such as non-union and graft resorption which required revision surgery. This is a retrospective study with limited sample size. Prospective study with larger sample size is justified to further prove these results.

Key Words:

Giant cell tumour of bone, distal radius, vascularised/ non-vascularised fibular graft

CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION

Giant cell tumour (GCT) of the bone is a benign tumour but can be locally aggressive. The tumour can be devastating to the bone which may result in severe deformity. They account approximately 4% to 5% of all primary bone tumour. It usually occurs at the age of 20 to 40 years old and slightly more common in females[1]. Distal radius being the 3rd most common location after distal femur & proximal tibia[2]. The tumour may remain dormant and only discovered incidentally, some will grow rapidly which lead to the destruction of cortex and extending to soft tissue. If untreated, it can metastasise to lungs and might lead to death from the complications of the disease[3]. They commonly presented with moderate pain near to the joint and associated with swelling[4]. About 10% presented with pathological fracture[1, 4].

In plain radiograph, GCT typically appear as a purely lytic lesion involving metaphysis and epiphysis regions, narrow zone of transition, may be expansile and even causing cortical break[1, 4]. It is widely classified using Campanacci grading system based on radiological findings. Grade I tumours has well-defined sclerotic border and intact bony cortex. Grade II has no sclerotic border, has a thin and expanded cortex with intact periosteum. Grade III tumours breach bony cortex and involve surrounding soft tissues[5].

Histology of GCT consists of mononuclear histiocytic cells, multinucleated giant cells and neoplastic stromal cells[6]. Treatment consists intralesional curettage with adjuvant therapies in grade I lesion[7-9]. Several adjuvant therapies such as phenol, liquid nitrogen, hydrogen peroxide and argon beam commonly used. The osseous voids after curettage then fill up with either bone graft or polymethylmethacrylate (PMMA)[8, 9]. For Campanacci III and some grade II usually treated by wide local excision followed by reconstruction using either VFG or

NVFG[1, 10, 11]. Wide local resection is recommended in grade III and some grade II for lower risk of recurrence[2, 12-14].

VFGs are frequently being used in grade III which involving more extensive resection of the tumour. A specialised team usually from plastic unit is required to deal with the VFG involving sophisticated works and skills. However, in centres which are lack of plastic surgeons, NVFG is being used and good outcomes were frequently reported. Therefore, we would like to know is there any difference in clinical outcomes between VFG and NVFG used in reconstruction of the wrist after resection.

1.2 OBJECTIVE

1.2.1 General Objective:

To assess the outcomes of vascularised versus non-vascularised proximal fibular grafting following wide local excision of distal radius giant cell tumour.

1.2.2 Specific Objective:

1.2.2.1 To evaluate and compare the outcome between vascularised and non-vascularised proximal fibular grafting based on Musculoskeletal Tumour Society score (MSTS).

1.2.2.2 To assess and compare the union (radiofibular) rates between vascularised and non-vascularised fibular grafting.

1.2.2.3 To evaluate the complications that may occur at recipient site (distal forearm) as well as the donor site (proximal leg) in patients who undergo vascularised and non-vascularised fibular grafting.

CHAPTER 2: MANUSCRIPT

2.1 ABSTRACT

Introduction

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The Overall MSTS score of NVFG was 80%, better than VFG 73.3% but statistically was not significant with the p-value of 0.60. In comparison of each component in MSTS scoring found to be no significant difference in pain ($p = 0.48$), function ($p = 0.94$), emotional ($p = 0.50$), hand positioning ($p = 0.61$), manual dexterity ($p = 0.93$) and lifting ability ($p = 0.89$). Median difference of union rate for VFG was 30 weeks (IQR = 31) while NVFG was 22.8 weeks (IQR = 23). There was no significant difference in union rate ($p = 0.52$) between these two groups of patients. However, two patients from NVFG group were reported non-union whereas all patients in VFG group achieved union. No serious morbidity reported at donor site from both groups.

Conclusion

Generally, VFG patients have larger tumour, hence more complicated surgeries. However clinical outcomes are generally similar compared to NVFG. VFG has slightly higher complication rates but they are considered minor whereas NVFG has serious complications such as non-union and graft resorption which required revision surgery. This is a retrospective study with limited sample size. Prospective study with larger sample size is justified to further prove these results.

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2.2 INTRODUCTION

Giant cell tumour (GCT) of the bone is a benign tumour but can be locally aggressive. The tumour can be devastating to the bone which may result in severe deformity. They account approximately 4% to 5% of all primary bone tumour. It usually occurs at the age of 20 to 40 years old and slightly more common in females[1]. Distal radius being the 3rd most common location after distal femur & proximal tibia[2]. The tumour may remain dormant and only discovered incidentally, some will grow rapidly which lead to the destruction of cortex and extending to soft tissue. If untreated, it can metastasise to lungs and might lead to death from the complications of the disease[3]. They commonly presented with moderate pain near to the joint and associated with swelling[4]. About 10% presented with pathological fracture[1, 4].

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using either VFG or NVFG[1, 10, 11]. Wide local resection is recommended in grade III and some grade II due to lower risk of recurrence[2, 12-14].

VFGs are frequently being used in grade III which involving more extensive resection of the tumour. Specialised teams including plastic reconstructive unit is required to deal with the VFG involving sophisticated works and skills. The advantages of VFG include early bony union by direct incorporation with native bone, fill up soft tissue voids after massive resection, lower risk of stress fracture and early return to function[10, 15]. However, in centres which are lack of plastic surgeons, NVFG is being used and good outcomes were frequently reported. Therefore, we would like to know is there any difference in clinical outcomes between VFG and NVFG used in reconstruction of the wrist after resection.

2.3 METHODOLOGY

This is a multicentre cross sectional study involving Hospital Universiti Sains Malaysia (HUSM) and University Malaya Medical Centre (UMMC). Patients who diagnosed with distal radius GCT and underwent wide resection followed by reconstruction with either autologous VFG or NVFG between year 2000 and 2019 in respective centres with minimum 1 year of follow up were included.

Exclusion criteria are previous trauma to wrist, congenital defect and radiotherapy over the operated wrist that could affect the functional outcomes. A total of 21 patients which fulfilled the selection criteria were enrolled in this study. Patients were invited to the outpatient clinic at respective centres once to evaluate the outcomes of operation. The clinical outcomes were evaluated using the musculoskeletal tumour society score (MSTS). Bony union of radius with fibular graft were evaluated by plain radiograph with at least three bridging callus in two views.

Data was analysed using SPSS software version 24.0. Statistical analysis of categorical data was presented as frequency and percentage while numerical data was presented as median and inter quartile range due to the data that was not normally distributed. Mann-Whitney U test was used for non-parametric data to compare MSTS score and bony union rate. Variables comparison with p-value less than 0.05 is considered as significant.

2.4 RESULTS

The overall demographic of total 21 patients were shown in Table I. There were 9 males and 12 females. The median age of presentation was 27 years old. Almost equal in number with regards to the side of the wrist involved; 10 were left sided and 11 were right sided. Involvement of the dominant hand seen in 11 patients. Of the 21 patients, 7 were VFG and 14 were NVFG. There were 14 (66.7%) patients Campanacci grade III and 7(33.3%) patients were grade II.

Demographic by types of graft was shown in Table II. The median age of patients presented with distal radius GCT were 27 (IQR=8) for VFG and 27 (IQR= 18.5) for NVFG. Of the 7 patients in VFG, 5 were male and 2 were female whereas in NVFG, 4 were male and 10 were female. There were 2 from VFG and 7 from NVFG had GCT on dominant hand. With regards to Campanacci grading, all patients from VFG were grade III whereas patients from NVFG having equal number of grade II and III. The duration of surgery was significantly longer in VFG with the median of 9.3 hours as compared to NVFG with the median of 2.5 hours. Hospitalization period was much longer in VFG with the median of 21 days whereas in NVFG with median of 4 days.

Results of MSTS score were analysed using non-parametric test called Mann-Whitney U test in view of the data were not normally distributed (Table III and IV). Overall NVFG scored 80%, better than VFG 73.3% but statistically was not significant with the p-value 0.6. In comparison of each component in MSTS scoring found to be no significant difference in pain ($p = 0.48$), function ($p = 0.94$), emotional ($p = 0.50$), hand positioning ($p = 0.61$), manual dexterity ($p = 0.93$) and lifting ability ($p = 0.89$).

Median difference of union rate for VFG was 30 weeks while NVFG was 22.8 weeks (Table V). There was no significant difference in union rate ($p = 0.52$) between these two groups of

patients. However, two patients from NVFG group were reported non-union whereas all patients in VFG achieved union.

Postoperative complications were slightly higher in VFG (42.9%) compared to NVFG (35.7%) (Table VI). In VFG group, 2 cases of post-operative venous thrombosis at anastomotic site, 1 wrist infection and 1 wrist subluxation on long term follow up while in NVFG , 2 cases of infection over operative site, 2 cases of wrist subluxation, 1 case of fibular head collapsed and 1 implant failure.

2.5 DISCUSSION

There are lots controversies regarding the use of autologous VFG or NVFG in reconstruction after the wide resection of distal radius. The main factor in deciding the use of VFG is extensive soft tissue extension of the tumour. VFG often harvest with its skin pedicle and this allow wound coverage after extensive wide resection to ensure adequate oncology margin. Wound can be closed without tension with osteocutaneous VFG and reduce post-operative wound breakdown and infection. It also allows the flexibility of tendon gliding for better function. Another added benefit of VFG is vessel follow through reconstruction technique whenever vessels need to be sacrificed. Second reason is the length of defect that need to be reconstructed. Usually defects larger than 5-7cm will consider using VFG for reconstruction[16, 17]. The VFG will undergoes hypertrophy, better bony union, less risk of graft resorption causing late fracture. Some authors would prefer using a VFG if resection of bone more than 6cm. However, the 6-cm rule remain controversial and unproven. A systematic review by Allsopp et al[18] found no compelling evidence to support the 6-cm rule.

In our series, length of grafts used ranged from 7.5cm to 16cm for VFG and ranged from 5.5cm to 9.5cm for NVFG. Most NVFGs were performed in UMMC due to lack of expertise in vascularised graft. Another important factor is the availability of the expertise to handle VFG. Even though the time of surgery is significantly longer in VFG but some authors strongly recommend its use for the benefit of early bony union, lower risk of graft fracture and early return to function[10, 11]. However, most published results were based on small number of case series.

In our studies, we include both wrist fusion and wrist reconstruction with either VFG or NVFG and assuming they will not affect the overall functional outcome as supported by previous study. Choo CY et al[19] compare the long term functional outcome in wrist fusion and wrist

reconstruction with proximal fibular grafts after resection of aggressive tumours of distal radius found no significant difference.

Our study revealed that there is no significant difference in MSTS score between VFG and NVFG groups. No similar study to compare the result to our knowledge. However, comparison on single arm results were comparable to other studies. Overall MSTS score for VFG was good 73.3% comparable to previous studies[11, 20]. NVFG scored 80% in our study and comparable to existing studies (73.3-93.3%) [21, 22].

Hiroshi Ono et al [11] reported a case series of total 7 patients with Campanacci grade II & III treated with vascularized bone graft published in 1997. The graft length ranging from 8 to 14cm. All cases united with the mean duration of 3.4 months. Functional outcome evaluated using MSTS scoring system reported good in 6 cases and 1 case with excellent result. None of them had recurrent disease with follow up ranging from 7 months to 11 years.

The disadvantage of VFG is duration of surgery was significantly longer with the median of 9.3 hours as compared to NVFG with the median of 2.5 hours. Duration of hospitalization also is longer in VFG with the median of 21 days while NVFG with the median of 4 days.

In this study, we found that bony union rate was better in NVFG (22.8 weeks) than VFG (30 weeks) but statistically no significant difference ($p = 0.52$). Theoretically VFG should achieved union earlier due to direct incorporation of a ‘live’ graft into native radius bone. NVFG on the other hand is a ‘dead’ bone which will become porotic and reduced mechanical strength leading to higher risk of stress fracture, resorption of graft result in structural bone collapse and later develop degenerative changes at fibular-carpal joint. Slow revascularization of the ‘dead’ NVFG occur by creeping substitution[10].

The possible reasons for delayed union in VFG are more extensive surgical resection and longer graft used in VFG. In addition, in VFG group all are Campanacci grade III whereas in NVFG group has equal number of Campanacci grade II & III. Another reason is that some of the patient may have developed thrombosis at anastomosis site much later post operatively and undetected. The thrombosed VFG will behave as NVFG and having similar healing process[10]. From previous reports, the time taken for radiofibular union varies greatly with wide range from 3 to 10 months[21, 22] (NVFG) and 2.5 to 9 months (VFG) [15, 23, 24].

Other factors need to be considered was that the radiograph was not performed at the same interval. As this was a retrospective study, timing of radiograph taken were not standardised. This will clearly affect the results because they could have achieved union earlier.

Non-union rate was observed higher in NVFG group. We have two patients from NVFG group having non-union whereas in VFG group all achieved union.

Overall percentage of complications are higher in VFG as compared to NVFG. Two patients from VFG group had venous anastomosis site thrombosis during early post-operative period and required urgent exploration and re-anastomosis of the graft. Both patients' graft survived after revision without any serious complications.

Although NVFG group having lower complications rate in our study, morbidity seemed to be higher; two patients reported non-union and one of them had osteomyelitis which required multiple debridement and revision surgery. Another patient from NVFG group had resorption of fibular head and subsequently the wrist joint subluxated which required revision and fusion of the wrist. Subluxation of wrist joint was reported 1 from VFG and 2 from NVFG groups. Infection rates over the wrist were similar in both group 14.3%. They were treated with antibiotics and later underwent wrist fusion.

2.6 CONCLUSION

Generally, VFG patients have larger tumour, hence more complicated surgeries. However clinical outcomes are generally similar compared to NVFG. VFG has slightly higher complication rates but they are considered minor whereas NVFG has serious complications such as non-union and graft resorption which required revision surgery. This is a retrospective study with limited sample size. Prospective study with larger sample size is justified to further prove these results.

2.7 LIMITATIONS AND RECOMMENDATIONS

In view of this disease is rare, the sample size of this study is small and may not reflect the actual outcomes. In order to increase the number of samples, more centres need to be recruited and longer duration of study is required.

The assessment of MTST score was not performed in the same timing post operation. A prospective study in future can overcome this problem by assessing the patient at the same time frame post operation.

The post-operative radiographs were not taken at the same intervals when we reviewed retrospectively. We recommend standardising the follow up and perform radiograph at same interval to assess bony union in future prospective study.

This study unable to compare the clinical outcomes according to Campanacci grading and length of the graft used. These two factors should be taken into consideration in future prospective study.

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2.9 TABLES

2.9.1 Table I: Demographic and Clinical Characteristics (n = 21)

Variable		n	(%)	Median (IQR)
Age (years old)				27.0 (14)
Type of Graft	VFG	7	(33.3)	
	NVFG	14	(66.7)	
Gender	Male	9	(42.9)	
	Female	12	(57.1)	
Dominant Hand	Right	21	(100.0)	
	Left	0	(0.00)	
Distal Radius of GCT	Left	10	(47.6)	
	Right	11	(52.4)	
Campanacci Grading	Grade 2	7	(33.3)	
	Grade 3	14	(66.7)	
Surgery Duration (hours)*				4.3 (6.4)
Hospitalization Period (Days)^				9.0 (16)
Duration of Union (Weeks)^				29.8 (26)

** Sample size n = 16*
^ Sample size n = 17

2.9.2 Table II: Demographic and Clinical Characteristics by type of graft (n=21)

Variables		VFG		NVFG	
		Median (IQR)	n (%)	Median (IQR)	n (%)
Age		27 (8)		27 (18.5)	
Gender	Male		5 (55.6)		4 (44.4)
	Female		2 (16.7)		10 (83.3)
Dominant Hand	Right		7 (33.3)		14(66.7)
	Left		0 (0)		0 (0)
Distal Radius GCT	Left		5 (50.0)		5 (50.0)
	Right		2 (18.2)		9 (81.8)
Campanacci Grading	Grade 2		0 (0)		7 (100.0)
	Grade 3		7 (50.0)		7 (50.0)
Surgical Duration (Minutes)*		9.3 (4.7)		2.5 (2.6)	
Hospitalization Period (Days)*		21 (4)		4 (5)	
Union Rates (Weeks)^		30 (31)		22.8 (23)	

**Sample Size; n = 16*

^Sample size, n = 17

2.9.3 Table III: MSTS Outcomes (n=21)

Variables	VFG, median (IQR)	NVFG, median (IQR)
Pain	5 (1)	5 (1)
Function	3 (1)	3.5 (1)
Emotional	4 (1)	4 (2)
Hand Positioning	4 (2)	4 (1.25)
Manual Dexterity	4 (1)	4 (1)
Lifting Ability	3 (1)	3 (1)
Total MSTS Score (per 30)	22 (3)	24 (5)
Total MSTS Score (%)	73.3 (10)	80 (16.6)

2.9.4 Table IV: Median Differences of MSTS Outcomes between VFG and NVFG groups (n=21)

Variables		Median (IQR)	U-stat	p-value*
Pain	VFG	5 (1)	41.0	0.48
	NVFG	5 (1)		
Function	VFG	3 (3)	48.0	0.94
	NVFG	3.5 (1)		
Emotional	VFG	4 (1)	40.5	0.50
	NVFG	4 (2)		
Hand Positioning	VFG	4 (2)	42.5	0.61
	NVFG	4 (1.25)		
Manual Dexterity	VFG	4 (1)	48.0	0.93
	NVFG	4 (1)		
Lifting Ability	VFG	3 (1)	47.5	0.89
	NVFG	3 (1)		
Total MSTS Score	VFG	22 (3)	42.0	0.60
	NVFG	24 (5)		
Total MSTS Score (%)	VFG	73.3 (10)	42.0	0.60
	NVFG	80 (16.6)		

**Mann-Whitney U Test*