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Comparision of the outcome of suprafacial and subfacial dissection of radial forearm in head and neck reconstruction

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Abstract

Purpose Radial forearm flap is a versatile and reliable tool in oral cancer reconstruction. However, a spectrum of donor-site deficits following harvest of this flap has been reported. Several surgical technique has been proposed to improve skin graft take and tendon exposure and subsequent undesirable results at donor site.

Objective The study was conducted to compare the donor-site morbidity associated with suprafacial radial forearm flap to that with subfacial donor site in oral cancer reconstructive surgery at our unit.

Methodology A total of 20 patients were included in the study and were categorized into suprafacial group and subfacial group. The donor-site morbidity was assessed both objectively and subjectively at 15 days, 1 month and 4 months postoperatively. The subjective evaluation was done using patient-related wrist elevation and patient and observer scar assessment. **Results** The suprafacial showed 80% of patients with complete graft uptake when compared to 50% in subfacial group and 20% showed delayed healing in subfacial group. Range of motion and grip strength was found higher in suprafacial group. Subjective evaluation revealed a better aesthetic out come in suprafacial group. The subjective evaluation for pain and function did not reveal a statistically significant difference between two groups.

Conclusion The study of donor-site morbidity clearly demonstrates the superiority of suprafacial technique over subfacial technique.

Keywords Radial forearm · Flap · Suprafascial · Subfascial · Goniometer · Dynamometer

Introduction

Radial forearm flap was first described in 1981 by Yang et al. [1]. It is considered as the new workhorse in micro-vascular reconstruction of various head and neck surgical defects [2]. It is a versatile and reliable tool in oral cancer

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¹ Department of Cranio-facial Surgery and Research Centre, S. D. M. College of Dental Science and Hospital, Dharwad 580009, India reconstruction. Much like its reliable and unquestionably useful pedicled predecessors (that is pectoralis major myocutaneous flap), the radial forearm has several distinct advantages. However, in common with all forms of local and distant flap reconstructions, these advantages have to be balanced against potential complications at the donor site. A spectrum of donor-site deficits following harvest of this flap has been reported. Compromised healing of the radial donor site is a significant cause of postoperative morbidity. Tendon exposure and adhesion formation cause delayed healing, poor cosmesis, and loss of function [3, 4]. Several surgical techniques have been proposed to improve skin graft take and tendon exposure and subsequent undesirable results at donor site.

Methodology

The study conducted was a prospective randomized in vivo study on patients reporting to our unit between 2010 and 2012 for head and neck reconstructive surgery. A total of 20 patients with oral carcinomas were included in the study and patients were randomly allocated to either of the following treatment group with tossing a coin.

Group 1: Ten patients who underwent reconstruction using suprafascial radial forearm-free flap (RFFF) (Fig. 1).

Group 2: Ten patients who underwent reconstruction using subfascial radial forearm-free flap (RFFF) (Fig. 2).

The donor-site outcome was collected prospectively, evaluated blindly by non-operative surgeon and analyzed

at 15 days, 1 month and 4 months postoperatively using both subjective questionnaire and objective functional measurements:

- 1. Subjective evaluation-
- a. Pain and function of donor site—using patient-rated wrist evaluation questionnaire (PRWE).
- b. Scar assessment—using the patient and observer scar assessment scale (POSAS).

The patient-rated wrist evaluation assessment form was downloaded from the internet and used for assessment (website—www.biomedcentral.com/content/downl oad/.../1471-2474-4-24-1.PDF).

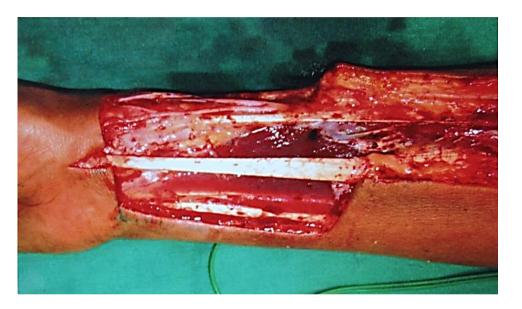
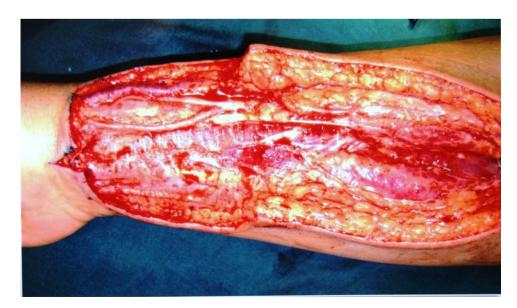


Fig. 1 Shows donor site following suprafascial dissection technique

Fig. 2 Shows donor site following subfascial dissection technique



The patient observer and scar assessment scale was downloaded from the internet and used for assessment (website—www.posas.org/wp-content/.../POSASv2-0_ ObserverScale-EN1.pdf).

2 Objective analysis was obtained using a standard goniometer and dynamometer

The values were analyzed statistically using *t* test, paired students two tailed *t* test, *N* par/Friedman's test.

Results

A total of 20 patients were included in the study. In ten patients, the radial forearm flap was harvested using a suprafascial dissection technique (group 1) and in another ten patients flap was harvested using subfascial dissection technique (group 2). The mean age of the patient was found to be 39.3 years (ranging from 25 to 55 years). Both group 1 and group 2 showed a male predominance with a male-to-female ratio of 8:2 in group 1 and 7:3 in group 2.

In group 1, the buccal mucosa was the site of the lesion in six patients and the tongue in four patients, whereas in group 2, lesions were seen involving the buccal mucosa in five patients and the tongue in five patients. All 20 patients included in the study were either in stage 3 or in stage 4 carcinoma. Histopathological reports revealed eight cases of well-differentiated squamous cell carcinoma and two cases moderately differentiated squamous cell carcinoma in group 1, whereas seven cases of well-differentiated squamous cell carcinoma and three cases of moderately differentiated squamous cell carcinoma were seen in group 2. The mean size of the defect in the oral cavity was 10.6 cm² in group 1 and 9.8 cm² in group 2, respectively. The mean size of the flap harvested was 46.9 cm² in group 1 and 47 cm² in group 2. In all patients, the donor site was closed using the split thickness skin graft from lateral thigh region.

Wound healing

In group 1, wound healing with complete take of skin graft was achieved in 80% of the patients (eight patients), while minor graft loss was seen in 20% of the patients (two patients) (Fig. 3). In group 2, wound healing with complete take of skin graft was achieved in 50% of the patients (five patients), while minor graft loss was seen in 40% of the patients (two patients) and major graft loss was seen in 10% of the patients (one patient) (Fig. 4).

In both group 1 and group 2, there was no incidence of tendon exposure in our study. There was a delayed healing in 20% of the patients in group 2.

Range of motion

In group 1 and group 2, all ranges of motion of wrist, that is pronation-supination, flexion-extension, and radial and ulnar deviation were reduced compared to normal values at 15 days, 1 month and 4 months postoperatively and were found to be statistically significant (P < 0.05). However, we observed that at 1st month follow-up in group 1 and 4th month in both groups 1 and 2, the values for ulnar deviation were found to be statistically insignificant. In addition, for group 1, the values for wrist extension and radial deviation at 4th month follow-up were insignificant. On comparison of range of motion between the two groups, we found that in group 1, all ranges of motion of wrist showed slightly higher values than compared to group 2 at 15 days, 1 month and 4 months postoperatively (Tables 1, 2, and 3); however, none of these values were found to be statistically significant in each follow-up. On



Fig. 3 Shows suprafascial donor site at 4 months postoperatively

Fig. 4 Shows subfascial donor site at 4 months postoperatively



Table 1Comparison of Rangeof Motion score between group1 and group 2 at 15 days,postoperatively

| Particulars | Group | Mean | S.D | Mean difference | <i>t</i> value | P value (95% confidence interval) |
|--------------------------|-------|-------|--------|-----------------|----------------|-----------------------------------|
| Flexion 15 days | 1 | 48.00 | 3.689 | 2.500 | 0.738 | 0.470 |
| | 2 | 45.50 | 10.055 | 2.500 | | |
| Extension 15 days | 1 | 42.00 | 7.528 | 1.000 | 0.205 | 0.840 |
| | 2 | 41.00 | 13.499 | 1.000 | | |
| Radial deviation 15 days | 1 | 12.50 | 2.635 | 3.000 | 1.857 | 0.080 |
| | 2 | 9.50 | 4.378 | 3.000 | | |
| Ulnar deviation 15 days | 1 | 22.00 | 3.496 | 3.500 | 1.878 | 0.077 |
| | 2 | 18.50 | 4.743 | 3.500 | | |
| Pronation 15 days | 1 | 68.00 | 4.216 | 2.000 | 0.600 | 0.556 |
| | 2 | 66.00 | 9.661 | 2.000 | | |
| Supination 15 days | 1 | 65.50 | 3.689 | 2.500 | 1.301 | 0.210 |
| | 2 | 63.00 | 4.830 | 2.500 | | |

Table 2Comparison of Rangeof Motion score between group1 and group 2 at 1 monthpostoperatively

| Particulars | Group | Mean | S.D | Mean difference | <i>t</i> value | P value (95% confidence interval) |
|--------------------------|-------|-------|-------|-----------------|----------------|-----------------------------------|
| Flexion 1 month | 1 | 65.00 | 6.992 | 4.000 | 1.309 | 0.207 |
| | 2 | 61.00 | 6.667 | 4.000 | | |
| Extension 1 month | 1 | 59.50 | 4.972 | 5.000 | 1.543 | 0.140 |
| | 2 | 54.50 | 8.960 | 5.000 | | |
| Radial deviation 1 month | 1 | 17.00 | 3.496 | 2.500 | 1.555 | 0.137 |
| | 2 | 14.50 | 3.689 | 2.500 | | |
| Ulnar deviation 1 month | 1 | 27.50 | 5.401 | 3.500 | 1.655 | 0.115 |
| | 2 | 24.00 | 3.944 | 3.500 | | |
| Pronation 1 month | 1 | 74.00 | 3.944 | 1.000 | 0.507 | 0.618 |
| | 2 | 73.00 | 4.83 | 1.000 | | |
| Supination 1 month | 1 | 71.00 | 2.108 | 1.500 | 1.342 | 0.196 |
| | 2 | 69.50 | 2.838 | 1.500 | | |

Table 3Comparison of Rangeof Motion score between group1 and group 2 at 4 monthspostoperatively

| Particulars | Group | Mean | S.D | Mean difference | t value | P value (95% confidence interval) |
|--------------------------|-------|-------|-------|-----------------|---------|-----------------------------------|
| Flexion 4 month | 1 | 73.00 | 6.146 | 2.000 | 0.775 | 0.449 |
| | 2 | 71.00 | 5.375 | 2.000 | | |
| Extension 4 month | 1 | 67.50 | 5.401 | 5.500 | 1.941 | 0.068 |
| | 2 | 62.00 | 7.149 | 5.500 | | |
| Radial deviation 4 month | 1 | 18.50 | 2.415 | 1.500 | 1.116 | 0.279 |
| | 2 | 17.00 | 3.496 | 1.500 | | |
| Ulnar deviation 4 month | 1 | 30.50 | 2.838 | 2.500 | 1.756 | 0.096 |
| | 2 | 28.00 | 3.496 | 2.500 | | |
| Pronation 4 month | 1 | 77.00 | 2.582 | 1.000 | 0.424 | 0.676 |
| | 2 | 76.00 | 6.992 | 1.000 | | |
| Supination 4 month | 1 | 74.00 | 4.595 | 3.000 | 1.701 | 0.106 |
| | 2 | 71.00 | 3.162 | 3.000 | | |

Table 4 Comparison of grip strength between group 1 and group 2 at 15 days, 1 month and 4 months postoperatively

| Particulars | ars Group Mean (difference between operated hand and non-operated hand) | | S.D | Mean difference | P value (95% confidence interval) |
|-----------------------|---|-----------|---------|-----------------|-----------------------------------|
| Grip strength 15 days | 1 | - 10.2000 | 4.39191 | - 0.70000 | 0.714 |
| | 2 | - 9.5000 | 4.00694 | | |
| Grip strength 1 month | 1 | - 4.1000 | 1.91195 | 2.0000 | 0.100 |
| | 2 | - 6.1000 | 3.10734 | | |
| Grip strength 4 month | 1 | - 2.4000 | 1.57762 | 1.50000 | 0.072 |
| | 2 | - 3.9000 | 1.91195 | | |

comparing with the same group using paired t test, at 1st and 4th month postoperatively, both group 1 and group 2 showed improvement in flexion, extension, radial deviation, ulnar deviation, pronation, and supination (wrist range of motion) to be statistically significant when compared to that at 15 days (Tables 1, 2, and 3). In addition, at 4th month follow–up, all ranges of motion values were close to normal values.

Grip strength

The grip strength was measured taking the non-operated hand as an internal control in both groups. A reduction in grip strength as compared to the non-operated hand was found in both group 1 and group 2; however, a comparison between the two groups showed better grip strength in group 1 than in group 2, but these values did not reveal statistical significant difference between the two groups at 15 days, 1 month and 4 months postoperatively (Table 4).

 Table 5
 Comparison of POSAS score between group 1 and group 2 at 4 months postoperatively

| POSAS | Group | Mean | S.D | Mean differ- ence | P value (95% confidence interval) |
|---------------|-------|-------|-------|----------------------|-----------------------------------|
| Observer | 1 | 26.10 | 2.025 | - 9.200 | 0.000* |
| score | 2 | 35.30 | 1.947 | | |
| Patient score | 1 | 19.30 | 1.889 | - 4.900 | 0.000* |
| | 2 | 24.20 | 2.530 | | |
| Total score | 1 | 45.40 | 3.307 | - 14.100 | 0.000* |
| | 2 | 59.50 | 3.837 | | |

*Significant value

Subjective assessment

POSAS questionnaire

The mean of observer score, patient score, and total score for

 Table 6
 Comparison of PRWE score between group 1 and group 2 at 4 months postoperatively

| PRWE | Group | Mean | S.D | Mean differ- ence | P value (95% confidence interval) |
|-------------|-------|-------|-------|----------------------|-----------------------------------|
| Pain score | 1 | 18.40 | 1.647 | 0.000 | 1.000 |
| | 2 | 18.40 | 1.713 | | |
| Function | 1 | 19.00 | 1.633 | 0.300 | 0.777 |
| score | 2 | 18.70 | 2.869 | | |
| Total score | 1 | 37.40 | 2.591 | 0.300 | 0.846 |
| | 2 | 37.40 | 4.040 | | |

group 1 showed a lower value than group 2 (Fig. 3) (lower value indicates better aesthetic results). A comparison of the above-mentioned scores between group 1 and group 2 at 4th month postoperatively showed a highly significant statistical value (Table 5).

PRWE questionnaire

A comparison of the pain score, function score and total score between group 1 and group 2, did not reveal any statistically relevant values (Table 6).

Discussion

Due to its consistent vascular pattern, long pedicle, pliable consistency, reliability, long pedicle, and relatively hairless volar wrist, the Radial forearm-free flap has become the most commonly used in postablative head and neck reconstruction. Although excellent closure results of the primary defect can be achieved, but prospective [3] and retrospective [4] clinical studies have shown that harvesting of the radial forearm flap can lead to functional, sensory, and aesthetic impairment of the hand at the donor site.

Various modifications have been achieved in an effort to improve these undesirable features, these primary closure using local flaps or "Z" plasties, full thickness skin grafts, splinting, tissue expansion, artificial skin graft or dermal matrix, negative pressure dressing, muscle coverage of exposed tendons by approximation of fascicles of the flexor pollicis longus and flexor digitorum superficialis [5], and types of dissection techniques like suprafascial or subfascial.

Direct closure of the radial forearm flap donor site is commonly considered as the method of choice if possible; it avoids the complication of delayed wound healing, but its application is restricted to narrow wounds. If the donor-site defect exceeds a range of 2–3 cm (depending on the elasticity of the tissue), direct closure is not possible without special approaches. 'Purse string' suturing technique has been used for reduction of donor sites when direct closure is not possible [6].

Local skin flaps are adjacent to the defect margin and can be considered for radial forearm-free flap donor-site closure when defect size is limited and when the elasticity of the surrounding tissue is sufficient. The Z-plasty technique has been described for the radial forearm-free flap donor-site closure by Hui et al. in 1999. It is based on a Z-shaped incision, which generates two opposing triangular flaps that are reunited after transposition, thus elongating the tissue and allowing direct coverage. However, although this method has distinct advantages, its application has not been reported for defects exceeding 4×5 cm [7]. Elliot, Bardsley, and colleagues have described closure of the radial forearm-free flap donor-site defect using a transposed ulnar fasciocutaneous flap and a V-to-Y flap technique for the proximal forearm. The donor defect is closed by a V-shaped flap, which is elevated as a fasciocutaneous flap based on the ulnar artery by V–Y advancement [4].

Another technique aimed at avoiding a skin graft that would cause an additional donor defect has been described by Hsieh et al., that is, radial forearm-free flap donor-site closure with a bilobed flap based on the ulnar artery perforators. The defect sizes in this range from 5×6 cm up to 8×8 cm, with an average defect of 47 cm^2 . The bilobed flap consists of a large lobe and a small lobe. After elevation, the flap is rotated, and the large lobe is used to cover the radial forearm donor defect, whereas the small lobe is used to repair the resultant defect from the large lobe [6].

Autologous skin graft like full thickness or split thickness skin graft has been used and found that both the grafts have the same short-term and long-term outcomes in the repair of the radial forearm-free flap donor sites. Zuidam et al. in his study found the same functional and aesthetic outcomes with both the grafts [8].

AlloDerm is a processed; a cellular, structurally intact dermal matrix derived from human cadaveric skin and can be used with or instead of split thickness skin graft or full thickness skin graft. Its main advantage is that no second graft is necessary, and therefore, no secondary defect is produced. AlloDerm has been compared with conventional split thickness skin graft and has been demonstrated that patients with allogeneic dermis take between 12 and 16 weeks to recover completely, whereas patients with split thickness skin graft are completely healed after 4–6 weeks. The prolonged healing period is a disadvantage, especially with respect to the special circumstances of already-weakened patients, as also shown in other studies [6].

The vacuum-assisted closure system has been suggested for use postoperatively as a bolster dressing over the split thickness skin graft. Andrews et al. have closely examined the procedure and show an increased incidence of small tendon exposures if the vacuum-assisted closure bolster is not left in place for a minimum of 6 days. Vacuum-assisted closure therapy has also been used to deal with tendon exposure after failed skin grafting. Subatmospheric pressure dressings stimulate the growth of granulation tissue over tendons and removes exudates from the wound, thereby contributing to improved graft adherence, which decreases donor-site morbidity [6].

The other alternative is tissue expansion which can be used to diminish the donor-site defect, so that direct closure can be performed. The major advantage of this technique is the possibility of direct wound closure after flap harvesting without the need for a skin graft. However, a major disadvantage of this procedure is the frequent rate of complications (up to 40%) including an increased risk of infections, temporary tissue hypoxia caused by pressure peaks after saline installation and implant extrusion, and the delay of approximately 20 days prior to cancer surgery itself when used pre-transfer [6].

As mentioned earlier, subfascial radial forearm-free flap is associated with marked donor-site morbidity, and to overcome this problem, suprafascial radial forearm flap was introduced by Webster and Robinson in 1995 [5]. As the deep fascia is preserved, it protects the tendons and the donor site remains covered with well vascularised deep fascia, thus preventing the exposure of tendons and faster uptake of skin graft. The research in suprafascial versus subfascial technique is mainly based on the retrospective studies and only few studies have investigated and compared different dissection techniques [6]. However, their clinical relevance remains controversial in the literature as studies evaluating donor-site morbidity have shown inconsistent results and limited information about patient perception.

Wound healing

Skin graft uptake

At the suprafascial donor site, Lutz et al. reported complete healing of 94% of grafts (98% of split skin and 84% of full thickness grafts) [9], with an overall incidence of only 6% graft loss, while Avery reported only a 4% graft loss in his study [10]. In our study, we found an incidence of 80% of patients with complete graft uptake with only 20% of the patients with skin graft loss; however, this included only minor graft loss that is < 10% of the total grafted area. Suprafascial donor site shows superior graft uptake and results in much lower incidence of delayed wound healing as compared to subfacial donor site.

Tendon exposure

Tendon exposure at subfascial site is reported as 28-13% [3, 4], whereas tendon exposure at suprafascial donor site is

3% as mentioned by Avery [10]. It is reported that the suprafascial donor site seems to be resistant to tendon exposure [11]. Tendon exposure is known to be a cause of delayed healing [4, 9].

Delayed healing

The mean time to wound healing is defined as a dry dressing not requiring any special dressing. In our study, the mean time of wound healing was 14 days. No cases of delayed wound healing were seen in suprafascial group, while 20% incidence of delayed healing was seen in subfascial group, where complete healing took more than 30 days. Delayed healing is not unusual at the subfascial donor site, where it has been reported as 28% [3] and 22% [4]. Toschka et al. reported an incidence of 11.4% of impaired wound healing, though it was not associated with decreased grip strength [12]. Our findings in this case are thus consistent with that reported in the literature [3, 4].

Functional assessment

Range of motion

In the present study, we observed reduction in range of motion of wrist, i.e., wrist flexion and extension, radial and ulnar deviation, and forearm pronation and supination of the operated hand compared to the normal values. A statistically significant difference was seen at 15 days; 1 month and 4 months postoperatively in both group 1 and group 2 when compared with normal hand.

We also compared all ranges of motion of wrist of group 1 and group 2 at 15 days, 1 month and 4 months postoperatively. We found that though the range of motion values in group 1 was slightly more than in group 2 at each interval of follow-up, a comparison between the two groups did not reveal a statistically significant value (always $P \gg 0.05$). This implies that functional morbidity in terms of range of motion of wrist at subfascial donor site is not significantly more when compared to suprafascial site. The data in our study are in line with the study conducted by Skoner et al. [13].

Grip strength

In the present study, an evaluation of the grip strength of the operated hand in each group was done taking the nonoperated hand as an internal control for each patient. It was found that though the grip strength in the suprafascial group was marginally better at each follow-up, a comparison of grip strength between group 1 and group 2 did not reveal a statistically significant value ($P \gg 0.05$). In addition, at the 4th month follow-up, the grip strength in the operated hand was found to be 71.4–95.5 and 76.9–100% that of the non-operated hands, in group 2 and group 1, respectively.

Our results for grip strength thus coincide with that reported in the literature: Boorman et al. report an average grip strength index for the operated hand as 84–99% that of the contra lateral hand [14]. Toschka et al. conducted a study, where they compared the hand function of dominant and non-dominant hand and found slight impairments regarding hand strength and mobility, but clinically, it was not significant [12].

Hence, in the current study, in terms of hand function (range of motion and grip strength), the suprafascial group shows higher values as compared to the subfascial donor site, thereby implying better outcome at this donor site. However, subfascial donor site does not show significantly higher morbidity rates as compared to the suprafascial donor site when analyzed statistically. Hence, hand function does not seem to be a major morbidity factor at either the suprafascial or subfascial radial forearm-free flap donor site.

Subjective assessment

POSAS questionnaire

With the POSAS questionnaire, we found that for group 1, the mean observer score was 26.10, mean patient score was 19.30, and mean total score was 45.40. For group 2, the mean observer score was 35.30, mean patient score was 24.20, and mean total score was 59.50. Thus, for all the scoring categories in group 1, that is, suprafascial donor site showed lower scores than that at the subfascial donor sites. A lower score for group 1 indicated a better cosmetic result in this group. Statistical evaluation also revealed a highly significant value for each scoring category (P = 0.000). We thus concluded that in the present series, patient satisfaction in terms of aesthetic appearance is significantly better for suprafascial donor site.

The results of subjective evaluation in the literature vary widely. One study reported 94.3% of patients rating the aesthetic outcome as fair or good [12], while Lutz et al. reported 98% of patients rating the aesthetic outcome as satisfactory [15]. Our study revealed higher patient satisfaction in terms of aesthetic appearance in the suprafascial group.

PRWE questionnaire

The PRWE scoring revealed the following results: for group 1, the mean pain score was 18.40, the mean function score was 19.00, and the mean total score was 37.40. For group 2, the mean pain score was 18.40, the mean function score was 18.70, and the mean total score was 37.10. Thus, the values of each scoring category in both group 1 and group 2 showed minimal differences. In addition, the comparison of

each scoring category did not reveal any statistically relevant values between group 1 and group 2. Thus, we found that patient satisfaction in terms of pain and function was similar for both suprafascial and subfascial donor sites. Sardesai and colleagues in their study found that patients reported worse function and increased pain; however, appearance did not seem to be an important factor [16]. Toschka et al. received a subjective rating of 80–100% by 88.6% of patients in their study when preoperative and postoperative hand function was compared [12].

Hence, in the current series, the results of the objective evaluation are validated with that of the subjective evaluation. Suprafascial donor site shows better healing and graft uptake resulting in lower incidence of complications and thereby better patient satisfaction in terms of cosmetics. However, in terms of hand function, both objective and subjective results in our study reveal no much difference in morbidity between the suprafascial and the subfascial donor sites.

Conclusion

The surgical method of suprafascial dissection for harvesting of radial forearm-free flap results in lower donor-site morbidity as compared to that of subfascial dissection. Suprafascial donor site shows superior graft uptake and results in much lower incidence of delayed healing as compared to subfascial donor site. Better healing at the suprafascial donor site results in lesser functional morbidity at the donor site; however, no much difference in functional morbidity was seen between the two groups on statistical analysis in our study. Subjective evaluation revealed greater patient satisfaction in terms of aesthetics at the suprafascial donor site, however, in terms of pain and function; patients in both the groups showed similar satisfaction.

Hence, we found that the surgical technique of suprafascial dissection is associated with minimal donor-site morbidity as compared to the subfascial dissection technique after harvest of radial forearm-free flap.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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