



Key to the Success of a Pedicled Latissimus Dorsi Musculocutaneous Flap in Patients with Soft Tissue Defects Around the Elbow Complicated by Trauma

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ABSTRACT

Objective: The purpose of this investigation was to evaluate the effectiveness of a pedicled latissimus dorsi musculocutaneous flap (PLDMF) applied to trauma-complicated large soft tissue defects in the upper extremity up to the elbow area.

Materials and Methods: Six patients who received a PLDMF at our clinic for a traumatic soft tissue defect around the elbow between 2014 and 2019 were included in this prospective follow-up, retrospective cohort-type analysis. In addition to the extent of the soft tissue defect, the length of postoperative hospitalization, follow-up, complications, and time to return to work, the patient's demographic information was also noted. The Q-DASH questionnaire was used to assess elbow and shoulder joint range of motion (ROM) 9 months after surgery.

Results: Six male patients with an average age of 39.8 ± 13.07 years had defects with a mean size of 272 cm^2 . In a patient who underwent amputation at the elbow level, a flap was used to treat an antecubital deformity after replantation in the same session. Three patients experienced hematoma in the donor location, superficial necrosis distal to the flap, and superficial infection. They were released after 14–29 days. The flaps survived in all patients, and both the Q-DASH questionnaire and shoulder and elbow joint ROM outcomes were satisfactory.

Conclusion: In complex soft tissue problems around the elbow joint that may need extensive therapy and would probably result in disability, a PLDMF can be used safely. Intraoperative Doppler ultrasonography helps prevent the most typical consequence, distal necrosis.

Keywords: Pedicle, latissimus dorsi, flap, musculocutaneous, defect, elbow

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INTRODUCTION

Large tissue defects present in upper extremity injuries, especially around the elbow, make reconstruction challenging for both the surgeon and the patient (1, 2). This is due to the fact that this type of damage presents more issues than just soft tissue coverage. Nevertheless, achieving a functioning elbow is a top priority. Bone or joint stability should be paired with appropriate and functional soft tissue coverage to restore elbow function (1–3).

Elbow abnormalities have been covered using a variety of techniques, including axial fasciocutaneous flaps, distal musculocutaneous flaps, free tissue transfer, and local random musculocutaneous flaps (1, 4–6). Covering huge and complicated flaws is far more challenging and time-consuming. The defined approaches could not be standardized because they differ from one another in both benefits and drawbacks. Especially in defects resulting from trauma, because the donor vessels are frequently present near the damage site, the surgeon may have difficulty deploying local flaps and free flaps for revascularization (1, 2). Additionally, it is necessary to take into account other approaches for complex elbow deformities, which due to their size cannot be covered with local flaps.

The latissimus dorsi (LD) is a potent and significant choice for wide elbow abnormalities because of its anatomically large structure and its capacity for remote transfer due to its neurovascular distribution (3, 7). It enables the complete length of the flap up to almost 40 cm to be obtained by dissection up to the axillary region (8). Due to the huge width of the vessels, a microscope is typically not required, making the procedure very simple and quick for the surgeon. Its success rate is high as a result of its robust vascularity. It is also resistant to infection. The most significant advantages of using a flap in this area over the other options are that the shoulder allows a functional reconstruction that contributes to the abduction and elbow flexion/extension movement and it can be performed in a single session (1, 9–12).

A pedicled latissimus dorsi musculocutaneous flap (PLDMF) can be successfully used to cover complex abnormalities of the arm, elbow, and antecubital and proximal forearm in a single-stage treatment with low donor site morbidity (1, 3, 9). Because of this, a PLDMF, which can cover the flaws properly and has high vascularity, contributing to healing of the fracture and providing functionality to the elbow joint, can be used safely.

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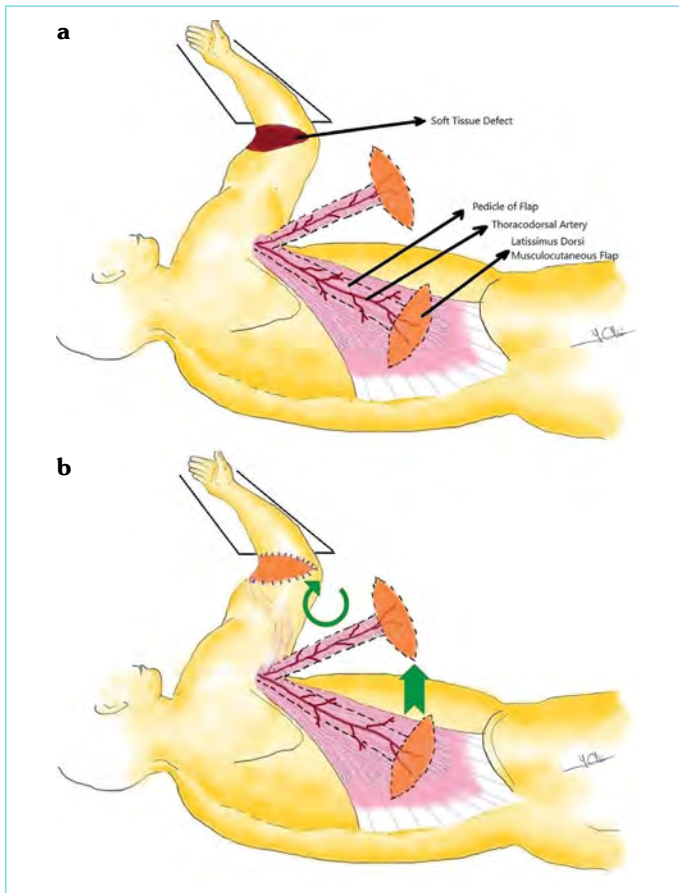


Figure 1. An anatomical view of the dissected PLDMF with landmarks and arterial supplies. (a) Schematic view of elevated latissimus dorsi musculocutaneous flap with its pedicle which can be advanced through the neck to the dorsal side of the elbow. (b) Schematic view of elevated PLDMF with its laterally rotated form around its longitudinal axis which allows the advancement of the flap to the antecubital region of the elbow

Despite some publications in the literature indicating that the complication rates of PLDMFs were high in defects extending to the forearm, on the other hand, some authors, on the contrary, have reported that it is an important surgical option with a low complication rate even for injuries involving the bones and joints around the elbow following high-energy trauma (2, 3, 12–15).

The purpose of the current study was to share our results obtained using the PLDMF, which we hardly ever use for traumatic complex elbow region injuries and which is described in a small number of patients in the literature but which can be a lifesaver for both the patient and the surgeon.

MATERIALS and METHODS

This prospective follow-up, retrospective cohort-type analysis was carried out by two orthopedic surgeons in our clinics. Six patients in whom a PLDMF was applied for a complicated soft tissue defect at the site of elbow/proximal arm injuries between 2014 and 2019 were included in the study. Ethics approval was obtained from the Kayseri City Training and Research Hospital Clinical Research Ethics

Committee (numbered 2020/120). Each patient gave their informed consent before enrolling in the study, and the investigation was carried out in compliance with the guidelines of the Declaration of Helsinki.

The patients were assessed in relation to age, sex, location of the defect, mechanism of damage, date of the injury, size of the soft tissue defect, length of postoperative hospitalization, follow-up, complications, and time to return to work. Nine months after the surgery, the Quick DASH (Quick Disabilities of the Arm, Shoulder, and Hand–Turkish edition) assessment form was used, and the joint range of motion (ROM) was compared to the opposite side upper extremity of the patients.

Statistical analyses of the data were performed using the Statistical Package for the Social Sciences (SPSS) 22.0. The frequency and percentages are provided in the evaluation of the data, and the relationship analyses were performed using Pearson's chi-square (χ^2) test. The level of statistical significance was set at a two-sided p-value of 0.05.

Surgical Technique

All surgical operations were performed using regional block anesthesia along with catheterization for postoperative analgesia and loupe magnification (2.5x). With the patient in the lateral decubitus position, after the limb was observed on the surgical arm board, the elevation of the LD musculocutaneous flap was planned from the ipsilateral field. Skin perforators were marked using Doppler ultrasonography. If necessary, aggressive debridement was performed to locate the problem region precisely. Mapping was carried out by measuring the size and shape of the defect on a sterile dressing.

The flap was noted so as to be 2 cm larger than the mapping. The muscle that Mathes and Nahai categorized as a class V muscle, making it appropriate for use as a flap to fill contralateral or distal abnormalities (16, 17), was removed from the inferior edge of the scapula following the incision stretching from the posterior axilla to the posterior iliac crest. Boucher et al. (7) showed that 80% of the LD can be adequately vascularized when the transverse branch of the thoracodorsal artery is intact. Subcutaneous dissection was carried out from medial to lateral according to that, as cutaneous perforators would be readily apparent close to the lateral border of the muscle. The vertical intramuscular branch of the thoracodorsal artery can be identified which emits two or three perforator branches to the skin (Fig. 1) (18).

Pedicle dissection was being done by preserving the thoracodorsal artery and nerve. In order to prevent skin and muscle separation and to enhance blood circulation, temporary sutures were inserted in the subcutaneous tissue and fascia at the corners with temporary sutures. The LD was removed by blunt dissection up to the teres major. The branches of the intercostal and lumbar arteries were ligated, and the thoracodorsal vessels and nerves were safeguarded. In the case of tightness in the pedicle, dissection was prolonged until the insertion of the LD. Then the musculocutaneous flap was rotated 90° around the neurovascular pedicle and moved from the tunnel created in the axilla to the recipient location (Fig. 2). Since large flaps will cause stress in the pedicle, the skin incision was performed distal to the tunnel. At this point, the blood flow in the pedicle was assessed using intraoperative Doppler ultrasonography (Huntleigh™ Dopplex DMX hand Doppler, UK). In the case of insufficient flow, the tunnel approach was dropped, and then axillary



Figure 2. The intraoperative, early postoperative and final views of the sample clinical case #2 in Tables 1 and 2. (a) The view of preoperative subtotal amputated right upper extremity at the level of the elbow before extensive debridement. (b) The view of the upper extremity after revascularization. (c) Usage of intraoperative Doppler ultrasonography. (d) The view of elbow joint fixation preparation with Schanz screw. (e) The view of PLDMF dissection and elevation. (f) The view of early closure of the donor side to reduce infection risk and also preparation of axillary region tunnel. (g, h) Early postoperative view of the elbow joint fixation and PLDMF. (i) The view of the second week delayed secondary closure of the forearm ulnar side plate screw fixation due to ulna shaft fracture operation incision and the restricted necrosis region at the endmost position of the PLDMF. (j) The view of the final clinical result

dissection was performed to advance the flap to the recipient site (Fig. 3). The procedure was resumed after checking the vascularity of the flap with Doppler ultrasonography. To restore M. Biceps Brachii function, the LD deep fascia was sutured using proximal and distal residues of the M. Biceps Brachii. After saturation of the incision lines and primary closure of the donor site, the operation was finished by checking the pedicle using Doppler ultrasonography. The donor and recipient locations of the flap were closed primarily after the drains were installed. In each patient in this investigation, a Penrose drain was applied at the recipient site for LD flaps.

Sample Clinical Case

In case #2 in Tables 1 and 2 and Figure 2, a 54-year-old male patient was hospitalized for surgery under emergency circumstances necessitating amputation at the right elbow level after an industrial crush injury caused by a conveyor belt. After performing arm revascularization and fixation with an external fixator, a PLDMF was scheduled for the 18x15 cm defect in the antecubital region. The flap was applied in the same session given the nature of the problem (Fig. 2). The external fixator was removed at 6 weeks after wound care. With proper physiotherapy,

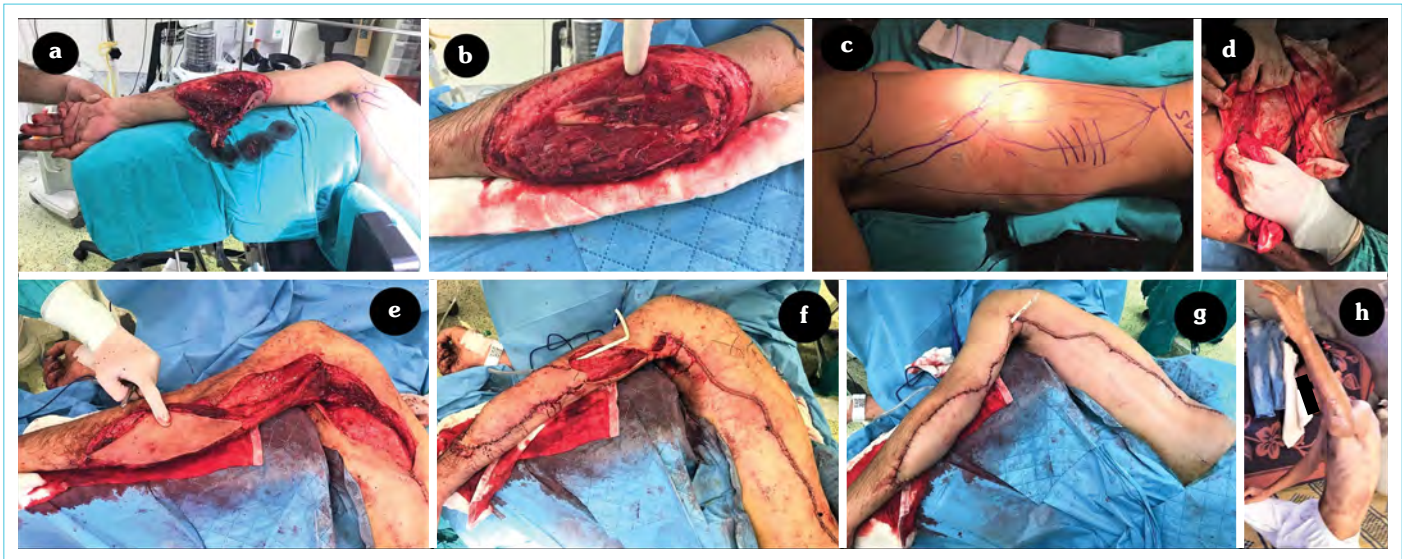


Figure 3. The intraoperative and final views of the clinical case #1 in Tables 1 and 2. (a) The view of preoperative soft and bone tissue deformity including one-third proximal end of the ulna and elbow joint. (b) The view of the defect after extensive debridement. (c) The view of PLDMF mapping and labeling to identify skin perforators using Doppler ultrasonography. (d) The view of PLDMF dissection and elevation. (e) After the blood flow in the pedicle was assessed by intraoperative Doppler ultrasonography, the inadequate flow was identified. Consequently, the tunnel method was dropped. The view of axillary dissection performed to advance the PLDMF to the recipient side. (f) The view of early closure of the donor side and suturation of the flap to the recipient side. (g) The view of the flap at the end of the surgery. (h) The view of the final clinical result

enough ROM was achieved in the elbow and wrist joints, and a triple tendon transfer was done to treat a radial nerve deficiency after 6 months.

RESULTS

Six patients (six males; mean age 39.8 ± 13.07 years) who had undergone PLDMF surgery were included in the study. While the defect size generated was 272 cm^2 (168 to 416), the defect of the patient who just had revascularization was in the antecubital region, and the others were in the dorsal region. The mechanisms of injury included two saw blade accidents, 2 motorcycle accidents, 1 conveyor belt accident, and 1 gunshot injury (Table 1).

While two patients were moved to a ward after being monitored in the critical care unit for 2 days postoperatively, the average operating duration was 268.8 ± 160.14 minutes (128 to 563), and mean hospital stay was 18.6 ± 5.31 days (14 to 29). Additionally, the patients had similar durations of return to work, i.e., 6.3 ± 2.73 months.

After hematoma occurred at the donor site in the sixth patient who was the firstly operated patient in the study, two drains were used routinely in the other patients, and this problem was not experienced in any others. In second patient, superficial necrosis formed distal to the flap and was treated with two rounds of debridement, leaving it to secondary healing. The sixth patient had a superficial infection that was treated with intravenous antibiotics and bandages while they were in the hospital. At the 6-week postoperative checkup, all flaps were still alive and the donor site was free of morbidity, and no further treatment was required.

There was no statistically significant change except second patient between the operated side and the counterpart side according to shoulder and elbow joint ROMs ($p > 0.05$) (Table 2). The Q-DASH score, by which functionality was assessed has a mean of 12.8 ± 10.22 (2.3 to 29.5) (Table 2).

DISCUSSION

The PLDMF is a lifesaving solution for the treatment of severe injuries affecting the bones and elbow joints, in addition to the extensive soft tissue flaws that many surgeons are concerned about when it comes to therapy. Its outcomes please both the patient and the surgeon. Doppler ultrasonography can be applied intraoperatively to avoid potential problems. If the surgical team is skilled and motivated enough to do so, it can be carried out even during the same session as revascularization like in our case #2.

Local flaps, pedicled radial forearm flaps, reverse lateral arm flaps, free tissue transfer, and LD flaps are employed for soft tissue abnormalities of the upper limb and elbow (16). However, if the defect is significant (150 cm^2), the alternatives are rather constrained (2, 3).

Although the LD flap is typically used for breast reconstruction after oncological surgery, it is also widely employed in the neck and distal arm region as well as for large defects of the elbow and proximal forearm (6, 14, 15, 19–21). Depending on the pedicle length, the PLDMF should be put up to distal of the olecranon. Jutte et al. (22) reported that anterior transposition up to 18 cm and posterior transposition up to 15 cm were successfully accomplished in a cadaver research. The most frequent side effect of the PLDMF is distal necrosis of the flap at the recipient site. To minimize this issue, it is advised that the flap should extend up to 3 cm from the

Table 1. Patients' characteristics

Patients (#)	1	2	3	4	5	6
Age/gender	32/M	54/M	48/M	19/M	37/M	49/M
Side	L	R	L	L	R	R
Occupation	Furniture carpentry	Laborer	Laborer	Motorcycle courier	Motorcycle courier	Accountant
Etiology	Industrial injury	Industrial injury	Industrial injury	Motorcycle accident	Motorcycle accident	Gunshot
Comorbidities	None	None	HT	None	None	DM
Soft and bone tissue wound characteristics	Open fracture of the olecranon with the bone defect of m. Triceps entesis region	Open fracture and dislocation of elbow joint with nearly amputated arm including only 2 cm skin island bridge intact	Open fracture of distal humerus and rupture of triceps with skin defect over the dorsum of the elbow	Abrasion of bone tissue located at the 1/3 proximal ulna with elbow capsular injury	Abrasion of humerus distal medial and elbow medial aspects without bone tissue damage but with ulnar neuropraxia	Skin defect over the dorsal side of the elbow without bone tissue defect or neurovascular damage
Defect size (cm)	26x16	18x16	22x15	18x14	16x16	14x12
Injury characteristics	Saw blade	Conveyor belt	Saw blade	Abrasion on the asphalt	Abrasion on the asphalt	Crush Injury
Reoperation after flap reconstruction	None	None	None	None	None	Hematoma drainage at the donor side
Follow-up period (months)	22	10	19	16	31	44
Flap complications	None	Medial side of the flap had 2x3 cm superficial necrosis	None	None	None	Superficial soft tissue inflammation
How to deal with the flap complication?	None	Secondary healing following superficial debridement	None	None	None	Treated with IV antibiotherapy
Hospitalization period (days)	14	17	17	19	16	29
Operative time (minutes)	267	563	155	314	186	128
Time to return to work (months)	4	8	5	4	6	11

HT: Hypertension; DM: Diabetes mellitus

olecranon, although Stevanovic et al. (1) found that it can be used safely up to 8 cm. The distal necrosis rate of the flap at the recipient side was reported to be 19% and 17% according to Stevanovic et al. and Hacquebord et al., respectively (1, 2).

Various iterations of the LD flap have been recorded over the years, with a growing number of applications (9, 16–18). Schwabegger et al. (23) described a flap with a vertical skin component that received only the descending branch of the thoracodorsal artery and a muscular strip containing the artery. This flap was the muscle-sparing latissimus dorsi (MSLD) flap, an alternative to the tho-

racodorsal artery perforator flap and other fasciocutaneous flaps. Since this definition, numerous articles have been published on the application of the MSLD flap in breast reconstruction (6, 24, 25). In 2011, Tan et al. (13) described a flap, in which they aimed to retain sensation by preserving the transverse branch of the nerve while sacrificing the arterial response of the flap by sacrificing the artery. With this dissection, the humerus location of the LD is unaffected. The skin paddle of the MSLD flap can be drawn in the horizontal, oblique, or vertical direction depending on the reconstruction. By leaving the transverse branch of the thoracodorsal nerve intact, the innervation of the muscle is retained. In this way,

Table 2. Q-DASH and ROM values of the patients

#	Q-DASH	Operated side ROM*				Non-operated side ROM*				p
1	6.8	Shoulder	Flex: 0–175	Ext: 0–55	Shoulder	Flex: 0–178	Ext: 0–60		>0.05	
			Abd: 0–174	Add: 165–0		Abd: 0–180	Add: 178–0			
		Elbow	In Rot: 0–58	Ext Rot: 0–82	Elbow	In Rot: 0–65	Ext Rot: 0–90			
			Flex: 10–125	Ext: 125–10		Flex: 0–135	Ext: 135–0			
			Pro: 0–74	Sup: 0–68		Pro: 0–80	Sup: 0–80			
2	29.5	Shoulder	Flex: 0–160	Ext: 0–60	Shoulder	Flex: 0–180	Ext: 0–60		0.042	
			Abd: 0–150	Add: 160–0		Abd: 0–180	Add: 180–0			
		Elbow	In Rot: 0–65	Ext Rot: 0–55	Elbow	In Rot: 0–65	Ext Rot: 0–90			
			Flex: 20–115	Ext: 115–20		Flex: 0–130	Ext: 130–0			
			Pro: 0–66	Sup: 0–74		Pro: 0–90	Sup: 0–90			
3	2.3	Shoulder	Flex: 0–160	Ext: 0–60	Shoulder	Flex: 0–180	Ext: 0–60		>0.05	
			Abd: 0–150	Add: 150–0		Abd: 0–180	Add: 160–0			
		Elbow	In Rot: 0–60	Ext Rot: 0–70	Elbow	In Rot: 0–70	Ext Rot: 0–90			
			Flex: 20–115	Ext: 115–20		Flex: 0–135	Ext: 135–0			
			Pro: 0–90	Sup: 0–70		Pro: 0–90	Sup: 0–70			
4	6.8	Shoulder	Flex: 0–160	Ext: 0–50	Shoulder	Flex: 0–175	Ext: 0–60		>0.05	
			Abd: 0–160	Add: 170–0		Abd: 0–170	Add: 180–0			
		Elbow	In Rot: 0–70	Ext Rot: 0–90	Elbow	In Rot: 0–60	Ext Rot: 0–90			
			Flex: 15–120	Ext: 120–15		Flex: 0–135	Ext: 135–0			
			Pro: 0–90	Sup: 0–90		Pro: 0–90	Sup: 0–90			
5	11.4	Shoulder	Flex: 0–160	Ext: 0–60	Shoulder	Flex: 0–160	Ext: 0–55		>0.05	
			Abd: 0–160	Add: 160–0		Abd: 0–180	Add: 180–0			
		Elbow	In Rot: 0–70	Ext Rot: 0–90	Elbow	In Rot: 0–70	Ext Rot: 0–90			
			Flex: 10–125	Ext: 125–10		Flex: 0–135	Ext: 135–0			
			Pro: 0–80	Sup: 0–80		Pro: 0–80	Sup: 0–80			
6	20.5	Shoulder	Flex: 0–180	Ext: 0–60	Shoulder	Flex: 0–180	Ext: 0–60		>0.05	
			Abd: 0–180	Add: 180–0		Abd: 0–180	Add: 180–0			
		Elbow	In Rot: 0–70	Ext Rot: 0–90	Elbow	In Rot: 0–70	Ext Rot: 0–90			
			Flex: 10–125	Ext: 125–10		Flex: 0–135	Ext: 135–0			
			Pro: 0–80	Sup: 0–80		Pro: 0–90	Sup: 0–90			

Q-DASH: Quick disabilities of the arm, shoulder, and hand; ROM: Range of motion; Flex: Flexion; Ext: Extension; Abd: Abduction; Int Rot: Internal rotation; Ext Rot: External rotation; Pro: Pronation; Sup: Supination

muscle atrophy is prevented and muscle length is maintained (2). Tan et al. (13) advise further suturing the distal end of the descending branch of the thoracodorsal nerve to preserve the majority of the motor function of the LD.

Similar to our patients, some individuals appear with severe injuries involving the bones and joints after high-energy trauma. Today, although free flaps are more widespread, it should not be forgotten that such intricate injuries are linked with neurovascular damage. Vein grafts are frequently necessary to put the anastomosis outside the damaged area. Additionally, more proximal dissection, use of microsurgical tools, and longer surgical time are required for end-to-side anastomoses (1). In situations where neurovascular systems are crucial for limb survival, additional anastomoses run the risk of raising failure or complication rates.

Additionally, several of these methods result in limitation of the shoulder and elbow joints' ROM. In their cadaveric study, Jutte et al. (22) discovered that the LD flap was ineffective for soft tissue covering in elbow area abnormalities. Sood et al. reported that following flap transfer, 98% of their patients were able to perform elbow flexion against gravity and 82.3% of them against resistance (19). Similar to our findings, other investigations in the literature have reportedly found conflicting evidence that the PLDMF is a functional flap, because it helps in flexion and extension of the elbow joint and abduction movements of the shoulder joint (2, 3, 9, 19).

Stevanovic et al. (1) used a musculocutaneous flap in only 5 patients in their study of 16, in which a pedicled LD flap was applied to the elbow for severe soft tissue abnormalities. The pa-

tients were followed up for an average of 23 months, and no flap loss was noticed throughout. The average defect was 100 cm², and 13 patients who experienced problems improved after a single session of surgery, while 3 patients needed extra intervention due to partial necrosis.

Choudry et al. (15), in a retrospective study conducted between 1988 and 2005, discovered that the etiology was trauma in half of 96 patients with flap-covered elbow abnormalities. Free tissue transfer was performed in 19 patients, while random local fasciocutaneous flaps were applied in 15 and pedicled flaps in 65. They used mostly radial forearm flaps and LD muscle flaps among the pedicled muscle flaps. In that research, while one or more problems developed in 30% of the patients, all failures occurred in patients who had pedicled flaps. However, when we examine previous research in the literature, we can observe that the complication rate is fairly low when pedicled flaps are used in line with the approach. The team doing the pedicle flap application should do a good job of preoperative planning in each instance. Marking the vascularity of the donor side of the flap with Doppler ultrasonography and sticking to these marks in the case are perhaps the most crucial aspects of this procedure to avoid failure. Additionally, similar to our patient #2, neither a radial forearm flap nor free tissue transfer would be appropriate since he had revascularization. The pedicled flap is the most sensible choice to take into account, as it will provide additional support for the vascularity of the revascularization level.

In PLDMF application, the flap is moved from the axilla to the defect area in two different ways. Although it is typically advised to use a subcutaneous tunnel, the flap can alternatively be conveyed expressly depending on the patient's subcutaneous tissue structure or the surgeon's experience (1, 2). As we have seen from our patients, the quantity of dissection is the most crucial element that determines the success of the tunnel approach. However, the most crucial factor that makes the PLDMF procedure safe with decreased complication rates compared to the literature is that we use intraoperative Doppler ultrasonography. If there is an issue in blood flow in the pedicle seen during examinations, it is simple to identify an intraoperative treatment. For instance, in our patient #1, the flap was primarily transferred by skin tunnel approach. In our assessment with intraoperative Doppler ultrasonography, because the blood flow was compromised, the axillary dissection approach was changed to pedicle viability. However, although the operation of our patient #2 was significantly more dangerous, no additional intervention was planned because the pedicle blood flow was triphasic according to the Doppler ultrasonography conducted after the tunnel technique.

Sydorak et al. (26) reported the average length of hospital stay of 13 days in patients with congenital diaphragmatic hernia surgically treated with the LD flap. DeLong et al. (27) said in a review that the hospital stay was on average 2.8 days in their trial where they employed the LD flap for breast reconstruction, which is one of the most popular uses. Although this time is a little bit longer in our study compared to the literature, we attribute this to the secondary treatment duration of our cases. It is evident that the duration of hospital stay will be shorter in cases performed under elective conditions rather than trauma cases.

There were certain drawbacks in the present investigation. First, creating a sample in a single center and from a specific region addressed by that center is not a multicentric study. Second, the number of cases was relatively small. Last but not least, the current investigation was carried out on those who had LD flap reconstructive surgery. Additional research is required, including comparisons with alternative flap choices.

CONCLUSION

The PLDMF is one of the safest and most effective treatments for severe complicated elbow injuries with significant soft tissue abnormalities. By using intraoperative Doppler ultrasonography and drains at the donor site, it is feasible to reduce the possibility of complications after surgery.

Ethics Committee Approval: The Kayseri City Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 09.07.2020, number: 120).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – KG; Design – KG, YE; Supervision – KG, YE; Resource – KG, YE; Materials – KG, YE; Data Collection and/or Processing – KG, YE; Analysis and/or Interpretation – KG; Literature Search – YE; Writing – YE; Critical Reviews – KG.

Conflict of Interest: The authors have no conflict of interest to declare.

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