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Anti-inflammatory effects of flap and lymph node transfer

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ABSTRACT

Background: Transfer of healthy tissue is commonly used in the treatment of complicated wounds and in reconstruction of tissue defects. Recently, microvascular lymph node transfer (LN) has been used to improve the lymphatic function in lymphedema patients. To elucidate the biological effects of flap transfer (with and without lymph nodes), we have studied the postoperative production of proinflammatory, anti-inflammatory, prolymphangiogenic and antilymphangiogenic cytokines, and growth factors (interleukin 1α [IL-1α], IL-1β, tumor necrosis factor α [TNF-α], IL-10, transforming growth factor β1 [TGF-β1], IL-4 and IL-13, and vascular endothelial growth factor C [VEGF-C] and VEGF-D) in postoperative wound exudate samples.

Methods: Axillary wound exudate samples were analyzed from four patient groups: axillary lymph node dissection (ALND), microvascular breast reconstruction (BR), LN, and combined LN and BR (LN-BR).

Results: The concentration of proinflammatory cytokines was low in all the flap transfer groups as opposed to the ALND group, which showed an extensive proinflammatory response. The level of anti-inflammatory and antifibrotic cytokine IL-10 was increased in the LN-BR group samples compared with the ALND and BR groups. In the LN and LN-BR groups, the cytokine profile showed an anti-inflammatory response.

Conclusions: Transfer of healthy tissue hinders the proinflammatory response after surgery, which may explain the beneficial effects of flap transfer in various patient groups. In addition, flap transfer with lymph nodes seems to also promote an antifibrotic effect. The clinical effects of LN in lymphedema patients may be mediated by the increased production of prolymphangiogenic growth factor (VEGF-C) and antifibrotic cytokine (IL-10).

1. Introduction

Surgery and trauma lead to tissue injury and wound healing, which in the early stages is dominated by a proinflammatory response, followed by proliferative and remodeling phases. The inflammation can persist abnormally in the presence of extensive trauma, insufficient circulation, infection or inflammatory disorders, resulting in abnormally healing

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wounds, unwanted scarring, and, in some patients, also lymphedema. Transfer of healthy tissue is commonly used in the treatment of complicated and chronic wounds [1,2]. Few studies have evaluated the inflammatory effects of flap transfer surgery used in breast reconstruction (BR). Microvascular BR has been shown to result in a greater systemic elevation of the acute phase inflammatory C reactive protein [3] and interleukin 6 (IL-6) [4] compared with local pedicular latissimus dorsi or lateral thoracodorsal BR flaps. However, both of these studies evaluated only the systemic response of surgery, and comparison to nonflap surgery was not performed. Thus far, little is known about the effects of flap transfer on the local wound healing environment.

More recently, autologous microvascular lymph node transfer (LN) has been used to improve the lymphatic drainage in lymphedema patients [5–7]. In addition to restoring the lymphatic flow, LN offers a possibility to retain the lymphatic, immunologic, and sentinel node functions of the affected limb. Interestingly, also flap transfer without lymph nodes (normal BR) has been shown to reduce the lymphedema symptoms of the arm in some postsurgical lymphedema patients [8–10]. This suggests that in some cases flap transfer alone modifies the local wound environment favorable to lymphangiogenesis.

Human lymph nodes express lymphatic vascular endothelial growth factor C (VEGF-C) [6], which is secreted into axillary wound exudate after microvascular LN [7]. Results from the preclinical lymphedema models using VEGF-C or VEGF-D have demonstrated the ability of these factors to induce the growth of new lymphatic vessels [11–13], thus providing a biological basis for the microsurgical LN method. Recent studies have shown that in addition to VEGF-C, lymphangiogenesis is regulated by a coordinated expression of proinflammatory and anti-inflammatory cytokines [14–16]. Furthermore, fibrosis and scarring are known to be key inhibitors of lymphatic regeneration [17]. Therefore, the factors affecting chronic inflammation and fibrosis are also a major topic of interest.

The clinical benefits of flap transfer surgery in various wound healing disorders are acknowledged [1,2], although there is lack of supportive biological evidence. To provide more information about the local biological and immunologic effects of flap transfer with and without lymph nodes, we decided to evaluate the postoperative production of proinflammatory cytokines (IL-1α, IL-1β, and tumor necrosis factor alpha [TNF-α]), anti-inflammatory cytokines (IL-10 and transforming growth factor beta1 [TGF-β1]), profibrotic cytokines (IL-4 and IL-13), and lymphatic growth factors (VEGF-C and -D) involved in wound healing and lymphangiogenesis in different patient groups: axillary lymph node dissection (ALND), microvascular BR, LN, and combined LN and BR (LN-BR; study design in Fig. 1).

2. Patients and methods

2.1. *Patient samples for cytokine analysis*

Permission for collecting patient samples was approved by the Ethical Committee of the Turku University Hospital. All patients signed an approval for sample collection and approved the use of their patient information in the study. Postoperative

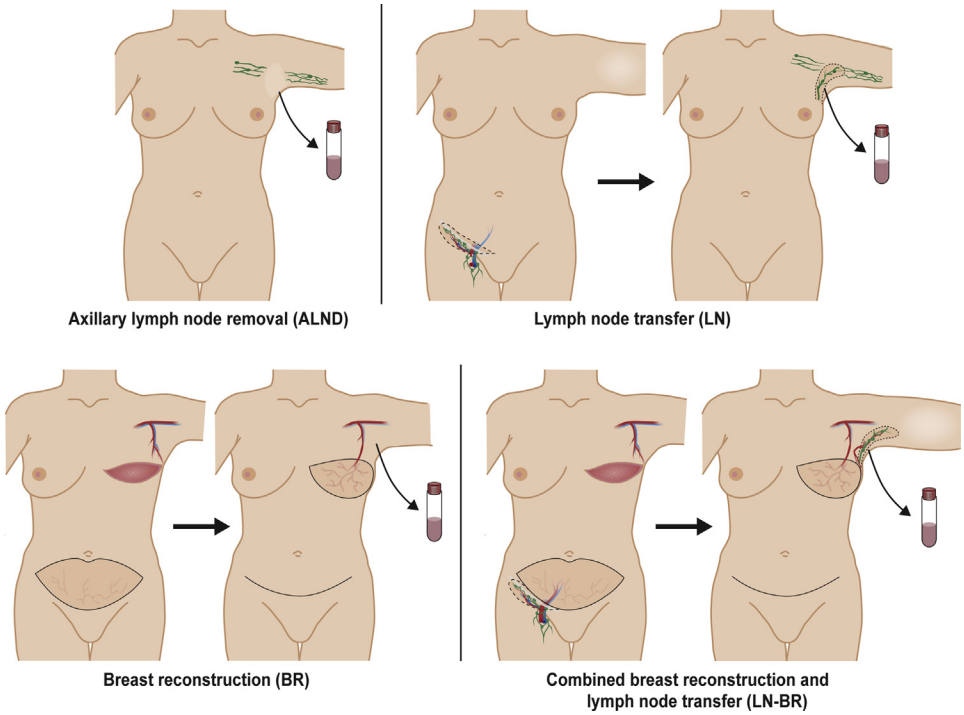

Fig. 1 – Patient groups for wound exudate samples are as follows: ALND, LN, BR, and LN-BR. Cytokines and growth factors analyzed from wound exudate samples are as follows: proinflammatory cytokines (IL-1α, IL-1β, and TNF-α), anti-inflammatory cytokines (IL-10 and TGF-β1), profibrotic cytokines (IL-4, IL-13), and lymphatic growth factors (VEGF-C and -D). (Color version of figure is available online.)