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ScienceDirect
EJSO
the Journal of Cancer Surgery
EJSO 41 (2015) 433–438
www.ejso.com

An investigation of lymphovenous communications in the upper limbs of breast cancer patients

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Accepted 10 November 2014
Available online 20 November 2014

Abstract

Background: Approximately 25% of breast cancer patients who undergo treatment to the axilla develop breast cancer-related lymphoedema (BCRL). The aim of this study was to test the hypothesis that lymphovenous communications (LVCs) open and act as a protective mechanism against the development of BCRL.
Methods: Five patients (Group 1) received intradermal injections of ^{99m}Technetium-labelled autologous erythrocytes into the 2nd ipsilateral hand webspace before and 6–12 weeks following axillary node clearance surgery (ANC). Ten patients at least three years after ANC were also recruited (Group 2); seven had developed BCRL and three had not. Blood was sampled from ipsilateral and contralateral antecubital veins 5, 15, 30, 60, 120 and 180 min post-injection to assess pre-nodal shunting from lymph to blood (LVCs), since nodes block erythrocyte transit. The proportion of activity remaining in the depot was used to calculate the degree of shunting in those with evidence of LVCs.
Results: Significant erythrocyte-bound activity, increasing over time, was detected contralaterally in 3 of the 5 patients from Group 1 (none of whom developed BCRL) and 3 of 7 patients with BCRL from Group 2, which indicated the presence of LVCs. The degree of shunting was more marked in those patients who did not develop BCRL compared with those who did.
Conclusions: The time-course of erythrocyte-bound contralateral activity indicates transit through lymphovenous communications rather than needle-induced trauma. Lymphovenous communications large enough to transmit erythrocytes are probably constitutional rather than induced. A larger study is warranted to assess any resulting protection against BCRL.

Keywords: Breast cancer; Lymphoedema; Lymphovenous communications

Introduction

All lymphatic fluid eventually drains into the venous system, primarily via the thoracic or lymphatic ducts in the neck. The existence of lymphovenous communications (LVCs) was first suggested by Threefoot in the 1960s and several animal and human studies have since shown the presence of LVCs, albeit in differing circumstances.[1–3] Studies have indicated the presence of communications between peripheral veins and peripheral lymphatics, although the functional significance of these lymphovenous communications (LVCs) remains unclear. It has been suggested that they open in response to lymphatic hypertension following axillary nodal surgery and provide a protective effect against lymphoedema.[4,5] Thus, local vascular clearance of lymph via peripheral LVCs would potentially diminish or prevent breast cancer-related lymphoedema (BCRL).

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http://dx.doi.org/10.1016/j.ejso.2014.11.036
0748-7983/

Clinical studies have been performed in patients with established BCRL, where they have undergone lymphatic reconstruction by creating anastamoses between lymphatic vessels and veins, lymph nodes and veins or proximal and distal lymphatics.[6] More recently, Boccardo et al. have performed lymphaticovenous anastomoses (LVA) between arm lymphatics and collateral branches of the axillary vein in breast cancer patients at the same time as axillary node clearance surgery (ANC) to attempt to prevent BCRL. This was a prospective randomised study in which the control group did not undergo lymphaticovenous anastomoses at the time of ANC, with 23 patients in each group. After 18 months follow-up, the LVA group had a lower rate of BCRL of 4.3% compared with the control group of 30.4%.[7] These studies have shown some promising results and our current study aims to further investigate the pathophysiology relevant to these experimental surgical interventions.

Previous work investigated the lymphatic transport of radiolabelled blood cells following intradermal and subcutaneous injection into the hand webspaces of 4 normal subjects.[1] No activity left the injection depot following subcutaneous injection. Following intradermal injection, however, scintigraphy revealed abundant axillary activity, indicating erythrocyte transport up arm lymphatics. There was no evidence of cell-bound activity in blood, showing firstly that erythrocytes become trapped in the nodes and do not pass through them into the bloodstream, and secondly that erythrocytes do not access the bloodstream through needle trauma.[1] A further study was performed in 4 patients 3 months after axillary surgery. Labelled erythrocytes administered intradermally were recovered bilaterally from peripheral venous blood (demonstrating the presence of LVCs) in the only patient in the group who did not go on to develop BCRL.[1] As this study assessed only small numbers of patients post-operatively, it was difficult to know whether the LVCs existed prior to surgery, or simply opened-up as a result of surgical intervention to the axilla. The current study aims to further investigate the presence or absence of LVCs in breast cancer patients and to see if these could act as a rescue mechanism in patients who do not develop BCRL.

Patients and methods

Two groups of patients were studied. For the first group, patients who were recently diagnosed with unilateral breast cancer and due to undergo surgery were recruited. The second group of patients had undergone axillary lymph node surgery for breast cancer at least 3 years previously. All patients gave written informed consent and the study was approved by a Research Ethics Committee (09/H0701/112) and Administration of Radioactive Substances Advisory Committee of the United Kingdom (ARSAC) (Certificate reference number RPC 204/2035/25873).

Patients studied pre-operatively (Group 1)

Five patients with recently diagnosed invasive breast cancer and due to undergo surgery, which included a level II/III axillary lymph node dissection (ALND), were recruited. Patients were studied pre-operatively and 2–6 weeks post-operatively, and subjected to the following procedures:

(i) clinical assessment of the upper limbs for presence of BCRL;
(ii) upper limb volume measurement using perometry;
(iii) lymphoscintigraphy and bilateral venepuncture of the upper limb to assess circulating erythrocyte ^{99m}Tc concentrations (calculated as % of administered activity) to assess for the presence of LVCs.

Clinical and upper limb volume assessments were also performed at follow-up visits, which ranged from 12 to 24 months post-surgery.

Patients studied post-operatively (Group 2)

Ten patients with invasive breast cancer diagnosed at least 3 years previously and who underwent level II/III ALND as part of their surgical treatment were recruited. Seven patients had developed lymphoedema post-operatively and 3 had not. Patients attended on only one occasion and underwent procedures (i)-(iii) as described above.

Radiolabelling of erythrocytes

For labelling with ^{99m}Tc, 1 ml heparinised whole blood was incubated for 5 min with stannous pyrophosphate (Mallinckrodt Medical, Petten, The Netherlands) containing 0.66 μg stannous chloride and then washed with 5 ml saline. An aliquot of 0.1 ml packed autologous erythrocytes was incubated with 250 MBq sodium ^{99m}Tc pertechnetate (Drytec; GE Healthcare, Bucks, UK) for 15 min and then washed twice with 5 ml saline. The ^{99m}Tc-labelled erythrocyte preparations were each reconstituted to a final haematocrit of 10% with saline. Labelling efficiency was 86.4 ± 10.2%.

Injection site and blood sampling

Patients in both groups were assessed for the presence of LVCs as follows. A 0.1 ml solution containing ^{99m}Tc-labelled erythrocytes (∼20 MBq) was injected intradermally into the 2nd webspace of the hand ipsilateral to the side of surgery. Venous blood samples (5 ml) were taken from the antecubital fossae of both upper limbs as soon as injection was complete (over 2 min), and further samples were obtained at 15, 30, 60, 120 and 180 min after injection.