

Indocyanine green utility in prevention and treatment of upper limb lymphedema

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ABSTRACT

Although screening tests have been widely implemented globally, there are still cases diagnosed with breast cancer in which radical mastectomy and axillary lymph node dissection remains the option of choice. In such cases significant alteration of the quality of life can occur especially in cases in which upper limb lymphedema develops. Therefore, attention was focused on determining the causes related to upper limb lymphedema as well as the therapeutic options in such cases. Special attention was given to the utility of indocyanine green for upper limb lymphatic preservation as well as for the utility of the method in treating this complication. This is a literature review regarding the possibilities of prevention and treatment of upper limb lymphedema by using indocyanine green.

Keywords: indocyanine green, upper limb lymphedema, breast cancer, axillary lymph node dissection, prevention

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INTRODUCTION

Breast cancer still represents the most common malignancy affecting women worldwide; the broad implementation of the national screening programs as well as the improvement of the imagistic techniques such as breast magnetic resonance or tomography conducted to an earlier diagnosis of this malignancy increasing the chances for the patient to benefit from conservative surgical procedures such as quadrantectomy and sentinel lymph node dissection. However, in a significant number of cases, the lesion is not suitable for conservative surgery and more aggressive procedures such as radical mastectomy and axillary lymph node dissection being required. Moreover, certain patients refuse to undergo adjuvant radiotherapy and therefore, a more extended surgical act such as total mastectomy is essential (1). In such cases the rates of postoperative complications are higher, upper limb lymphedema being one of the most fearful complications. In the meantime, we should not omit the fact that upper limb lymphedema probably impedes most the quality of life in breast cancer survivors. In this respect, attention was focused on identifying the pathogenesis of this complication as well as the possibilities of prevention and treatment (2,3).

PATHOGENESIS OF UPPER LIMB LYMPHEDEMA

Defined by the presence of an excessive fluid at the level of the upper limb after breast cancer surgery or radiotherapy, upper limb lymphedema has been reported initially by Halstead in 1880 being a common finding after ultra-radical surgical procedures (4-6). This complication was usually related to the impaired capacity of transport of the upper limb lymphatics after en bloc removal of these structures including a significant number of lymph nodes (2,3). While at that moment upper limb lymphedema was rather the rule after radical surgical procedures, once the surgical techniques improved the rates of this complication decreased, nowadays being estimated that less than 20% of cases will experience such side effects, the maximal incidence being at two years postoperatively (7). However, it seems that not only the extent of the surgical procedures influences the risks of further upper limb lymphedema but also does the peritumoral lymphovascular invasion or extranodal extension of the affected lymph nodes (8). It has been demonstrated that genetic alterations can be also related to the risk of upper limb lymphedema development (9-11).

THE ROLE OF INDOCYANINE GREEN IN PREVENTION AND TREATMENT OF UPPER LIMB LYMPHEDEMA

The method was initially imagined due to the fact that a significant number of patients undergo-

ing curative intent breast surgery including axillary lymph node dissection will experience at a certain moment of their evolution upper limb lymphedema (12). The dimensions of the upper limb edema can widely vary from a difference of a few millimeters between the two arms to centimeters; this complication can significantly alter the quality of life of these patients and can further induce the development of other loco-regional complications. Indocyanine green injection seems to play a crucial role in both prevention and treating upper limb lymphedema after axillary lymph node dissection (12-14).

Concerning to the role of indocyanine green injection in preventing the development of upper limb lymphedema, it is based on its capacity of revealing the lymphatic collaterals of the arm during lymph node dissection and in this way preserving them. If indocyanine green is injected intradermally before beginning the axillary lymph node dissection, the molecule will bind to local albumin and is further absorbed in the lymphatic network (14). Further on, illumination of the operative field with diode light will excite indocyanine green molecules and will lead to the apparition of near infrared fluorescence which is filtered and recorded by using a camera. The images obtained in this manner will provide valuable information regarding the local anatomy and disposition of the lymphatic network and will provide for the surgeon a clear perspective of the lymphatics at this level; the method has recently gained popularity offering the oncological surgeon the chance to provide an accurate axillary lymph node dissection without harming the surrounding lymph vessels and therefore, without inducing the risk of upper limb lymphedema (15-17).

Moreover, certain authors observed that upper limb lymphedema also might occur after conservative axillary surgical approach such as sentinel node biopsy. In this respect, the Japanese authors conducted by Sakurai et al. (18) conducted a study on 372 patients, candidates for sentinel node biopsy for breast cancer; in all cases the authors used indocyanine green injection in order to study the lymphatic mapping of the upper limb as well as to determine sentinel node. Furthermore, the authors observed that in 76 cases the upper limb lymphatic drainage was at the level of the sentinel node; however only five of these patients developed upper limb lymphedema. Among the cases in which the upper limb lymphatic pattern did not cross the sentinel node, none of the patients further developed upper limb lymphedema after sentinel node biopsy. The authors emphasized the fact that this method is a reliable one in order to identify cases at risk for upper limb lymphedema development.

THE ROLE OF INDOCYANINE GREEN IN UPPER LIMB LYMPHEDEMA DIAGNOSTIC AND PREVENTION

The initial diagnosis of lymphedema is established through a basic method consisting of using a measuring tape and determining the diameters of the limb around the wrist, 10 cm distal to the elbow, around the elbow and 10 cm proximal to the elbow. A difference of at least 5% between the affected and non-affected arm is considered as a significant one in order to establish the diagnostic of lymphedema and to consider that the patient has a lymphatic dysfunction (19).

In cases in which upper limb lymphedema already develops, indocyanine green injection is also useful in order to provide a proper staging of this entity. Certain authors proposed subcutaneous injection of indocyanine green at the level of the upper limb followed by infra-red visualization of the patterns of spread; in cases presenting a normal lymphatic drainage, a linear pattern of spread is encountered. According to these authors, linear pattern is encountered in patients with stage 0 to stage IV lymphedema, splash pattern is encountered in stage I lymphedema in association with the linear one, stardust pattern is encountered in stage II, III and IV also in association with the linear pattern while in stage V lymphedema stardust or diffuse pattern is encountered. In order to differentiate stages II, III and IV, attention should be focused on identifying how many regions are affected: in stage II cases a single region is affected, in stage III cases two regions are affected while in stage IV cases three regions present the features of lymphedema (20-22).

INDOCYANINE GREEN AS PART OF THE THERAPEUTIC STRATEGY FOR UPPER LIMB LYMPHEDEMA TREATMENT

Indocyanine green is not only used for upper limb lymphedema diagnostic, staging and prevention but also in treating this pathology. Recent studies managed to demonstrate that indocyanine related lymphography is useful in order to establish the stage of the dysfunction, the indication for lymphovascular anastomosis, the identification of the suitable vessels in order to create the anastomosis and the evaluation of the patency of the created anasto-

mosis (23). Depending on the stage of affection, the therapeutic option will be chosen. Therefore, in cases in which stage I to IV upper limb lymphedema is encountered, lymphovascular indocyanine green guided anastomosis can be performed in order to diminish the volume of lymph at the level of the lymphatic vessels; in cases presenting stage V lymphedema microvascular surgery is no longer effective due to the fact that severe lymphatic sclerosis already developed (20-22). Thus, is easily to understand why a simple anastomosis could not improve the status of the lymphatic network.

In order to establish which lymphatic vessel is most suitable for a lymphovascular anastomosis, indocyanine green should be injected at the level of the above-mentioned sites before skin incision is performed in order not to section the subcutaneous network and to impede the migration of the tracer.

An interesting study conducted on this issue has been recently published by Akita et al. and included 26 cases with upper extremities lymphedema in which standard lymphoscintigraphy and indocyanine green lymphography was performed. The authors came to demonstrate the efficacy and superiority of the indocyanine green based lymphography when compared to standard lymphoscintigraphy in identification of the dilated lymph vessels, in anastomosis creation and in the verification of the patency of the newly created anastomosis; the latter aspect represents one of the most important benefits of indocyanine green administration due to the fact that it can offer a real time validation of the anastomosis functionality (24).

CONCLUSIONS

Indocyanine green lymphography represents an important diagnostic and therapeutic tool in order to assess the stage of the upper limb lymphedema after both sentinel node and axillary lymph node dissection in breast cancer patients. In such cases, after demonstrating the presence of this complication, indocyanine green injection is useful in order to identify the dilated lymphatic vessel, to create the anastomosis between the lymphatic vessel and the corresponding vein and, finally, to verify the patency and the good functionality of the anastomosis.

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