"LOCAL COMPLICATIONS OF PERIPHERAL INTRAVENOUS CHEMOTHERAPY – ANALYSIS IN CARCINOMA BREAST PATIENTS"

Dr. Tushar M. Parmeshwar¹, Dr. Dilip Gupta², Dr. Rutuja Darokar³

¹(MS Surgery, DNB Surgery) Assistant Professor Dept. of General Surgery MGIMS and KHS Sevagram Wardha Maharashtra.

²(MS Surgery) Director, Professor and HOD Dept. of General Surgery MGIMS and KHS Sevagram Wardha Maharashtra.

³(MBBS) Dept. of General Surgery MGIMS and KHS Sevagram Wardha Maharashtra. 442102

Article Info: Received 18 September 2019; Accepted 10 October 2019

DOI: <https://doi.org/10.32553/ijmbs.v3i10.603>

Corresponding author: Dr. Dilip Gupta

Conflict of interest: No conflict of interest.

Abstract

Aims: To identify and record the local reactions at the site of IV cannula in women with carcinoma breast during peripheral intravenous chemotherapy treatment. To find out the incidence of these reactions and correlations with various factors.

Method- Prospective Observational Study was done with evaluation of 559 individual peripheral intravenous chemotherapy cycles given in carcinoma breast patients from June 2013 to September 2015.

Results: 1 in every 5 carcinoma breast patients receiving peripheral intravenous chemotherapy developed local complications. (20.92% in adjuvant cases and 18.55% in neoadjuvant cases). Pain followed by induration and altered skin color were the most common complications. Extravasation was present in 6.44% cases. Other complications commonly noted were tingling sensation in IV applied limb, edema, thrombophlebitis, cellulitis and ulcer. IV cannula application on ipsilateral site (in limb on side of breast cancer) is associated with RR=2.08. IV cannulation over the wrist have 1.57 times (RR=1.57) and multiple puncture attempts to secure IV cannula is associated with 1.97 times (RR=1.97) more risk of developing local complications following peripheral intravenous chemotherapy. Elderly age >50yrs, small of large calibre IV cannula (no 18 G and No 24 G) have more local complications.

Conclusions: Occurrence of local complications after peripheral intravenous chemotherapy in carcinoma breast patient is common. Vigorous monitoring of patient with repeated and frequent examination of site of chemotherapy cannulisation must be done during the complete chemotherapy infusion process and detailed records must be kept at every stage. A generalised chemotherapy infusion guidelines and protocol should be established according to the hospital occurrence. Active Patients participation in monitoring is advised. More multicentre studies are required to create a data base of venous damage occurring following intravenous peripheral chemotherapy and to formulate standard guidelines and protocols to reduce the rate of complications. Precaution, and care during peripheral intravenous chemotherapy can prevent development of local complications and remove the need for surgical intervention for management of the complications, thus, reduce the hospital stay, additional diagnostic procedures and treatment, stress in the life of the patients' relatives, extra work load on the health personnel and economic loss accordingly.

INTRODUCTION:

One in ten of all new cancers diagnosed worldwide each year are a cancer of the female breast and it is the most common cancer in women today in both developing and developed countries. It is also the principal cause of death from cancer among women globally⁽¹⁾. Today the approach to a case of breast carcinoma is considered multidisciplinary. Surgery is no longer considered the ultimate and combination therapy is advocated. Chemotherapy has become a very essential component for planning the treatment of the breast carcinoma and according to NCCN

guidelines⁽²⁾; chemotherapy is indicated in almost all stages of breast carcinoma in one capacity or the other. The most commonly used route for chemotherapy is intravenous and therefore, venous access is indispensable. There is a propensity for complications of peripheral venous access routes, hindering the progress of treatment. The toxic properties of chemotherapy agents amplify complications at the site of venous access. Although the occurrence of extravasations is little reported, a large number of patients are at risk of this occurrence, since vesicant drugs are often administered as chemotherapeutic

agents.⁽³⁾ Occurrence of a local complication may result in physical deformities and many of them require surgical intervention. It increases both hospital stay and cost of treatment, and the physical and psychological sufferings of the patient are amplified. Moreover, maximum of these complications are preventable through precaution, early detection and care, and may help in reducing the need for surgical interventions.

Intravenous Chemotherapy in Carcinoma breast patients is a complex process in health care. Errors may constantly occur at various stages. These errors bring significant harm to patient ^(4,5) who is already weakened by the disease and the treatment. There is limited data in national and international literature related to venous network damage and local complications occurring during intravenous chemotherapy in carcinoma breast patients.

MATERIAL AND METHODS

The present study was a prospective observational study conducted in the Department of Surgery at Mahatma Gandhi Institute of Medical Sciences a rural medical college and hospital of central India from June 2013 to September 2015 after the clearance from Ethics committee of the Institute.

During the study period 140 new females were diagnosed with breast cancer out of which 121 female breast cancer patients received 691 chemotherapy cancer. One peripheral intravenous chemotherapy cycle given for carcinoma breast was considered as one case. If same patient was admitted for next cycle of chemotherapy, she was included in the study as a separate case for observation. Some of the patient receiving chemotherapy did not full fill the inclusion criteria, did not consent for the study, were lost to follow up, or received radiotherapy and hence excluded. Those patients who already developed complications and where not completely treated were kept on follow up and not included as new cases. Hence, a total of 559 cycles out of 691 were taken as cases under observation in our study (Table 1). Each cycle was included as a separate case and was evaluated individually independently and separately from previous or subsequent chemotherapy cycles. Case details, chemotherapy details and procedure of IV access and infusion was observed and recorded for each case in the study. These patients were observed during the chemotherapy infusion for reactions at the local site. These patients were followed up at 2 weeks following the chemotherapy, during their routine

follow up visit at Surgery OPD or at Radiotherapy OPD. Follow up information was also being retrieved from Hospital information system. Patients who did not follow up even after repeated contacts were excluded from the study.

RESULTS

Out of total 559 cases included in the study, 435(77.82%) received adjuvant chemotherapy and 124(22.18%) received neoadjuvant chemotherapy. Amongst the total 559 cases included in the study, 114 developed some sort of local complication accounting for 20.30 % of the total cases undergoing chemotherapy. In adjuvant group 20.92% of patients developed local complication whereas in neoadjuvant group the corresponding value was 18.55%. Amongst the total cases, pain was the most common complication of peripheral intravenous chemotherapy occurring in 9.30% of cases followed by induration in (7.16%). Extravasation occurred in 6.44% of patients. Ulcer occurred in 2.68% of cases. The perimenopausal age group (41-50 years) is the commonest age group of breast carcinoma, comprising 40.3% cases of our study.

The mean age in the study group was 46.47±10.11. In adjuvant group 27.59% cases between 61-70 yrs. developed complications and 26.92% between 51-60 yrs. in neoadjuvant group. There is no significant difference in the occurrence of local complication in adjuvant and neoadjuvant cases in our study During adjuvant therapy CEF was the preferred regimen therapy accounting for 45.29% whereas during neoadjuvant therapy PE was preferred regimen accounting for 50.82% of neoadjuvant cases. Anthracycline based CEF chemotherapy regimens had more complications (in 25.38% adjuvant and 25.81% neoadjuvant cases) compared to other regimens. Only 3.04% (17 cases) had an IV access placed on the same side as that of the malignancy of the breast. IV cannula application on ipsilateral site is associated with 2.08 times (RR=2.08) more chances of local complications following peripheral intravenous chemotherapy. Maximum number of patients 81.57% (456 out of 559) received no 22 cannula for IV access. Local complications developed in 19.71% with 22 gauge cannula whereas 33.33% with 18G and 23.25% with 24 G IV cannula in adjuvant group. And with 20 gauge IV cannula, 27.27% of adjuvant cases had complications. Dorsum of hand was the most preferred place of intravenous cannula insertion accounting for 80.50% (450 out of 559). IV cannulation over the wrist

have 1.57 times (RR=1.57) more risk of developing local complications as compared to other sites in our study (30.61% cases had complication with cannula crossing wrist joint v/s 19.41% at other sites). 14.13 % (79) of the total cases (n=559) required more than one attempt to secure IV access. Multiple puncture attempts to secure IV cannula is associated with 1.97 times (RR=1.97) more chance of developing local complications following peripheral intravenous chemotherapy. (Complications in 36.84% cases with multiple attempts v/s 17.92% complications with single attempt IV cannulation).

DISCUSSION

Even after all precautionary methods complications occur following peripheral intravenous chemotherapy in a significant number of cases. In the study, distribution of breast cancer in accordance with the epidemiology of breast cancer.⁽⁶⁾ Local complications following peripheral intravenous chemotherapy were most common in Old age (> 50yrs.) Old age people have fragile veins, skin becomes paper thin, loses tone and elasticity, there is loss of subcutaneous fat, have multiple medical problems and weak immune system which increases the risk of local complications following peripheral intravenous chemotherapy⁽⁷⁾

Surgery followed by chemotherapy was the most commonly followed protocol among cases included in this study. This finding indicates that most patients are being diagnosed at an earlier stage of cancer, having operable malignancies (stages I, II, IIIa). There is no significant difference in the occurrence of local complication in adjuvant and neoadjuvant cases in our study.

In the study, the various local complications occurring after peripheral intravenous chemotherapy include pain, edema, and tingling sensation over IV arm, extravasation, induration, alteration of skin color, thrombophlebitis, cellulitis, and ulcer. 1 in every 5 patients receiving peripheral intravenous chemotherapy developed local complications. (20.39% cases). The complications at venous sites may be considered high, due to consequences caused in aesthetic, physical, psychological and emotional terms. Martins *et al*⁽⁸⁾ had complications in 17.1% of neoadjuvant and 22.4% of their study patients. In a study conducted by Marshall-McKenaa⁽⁹⁾ *et al*, out of 110 patients in their study, 65 patients (59.09%) reported arm symptoms during chemotherapy. These aspects overlap with the fact that the women are facing a disease marked by the stigma surrounding

their treatment and prognosis, emphasizing alterations in their self-image and self-esteem.

Pain is approximately present in 1 in every 10 patients receiving chemotherapy and is the most useful symptom to recognise the possibility of complication (9.30% of total cases). The first sign of possible leakage of drugs into the tissues is pain and discomfort⁽¹⁰⁾ and also the most useful symptom to alert the administrator to the possibility of further complication⁽¹¹⁾. Those with high anticipatory anxiety and expectation of significant pain have been found to over-predict the degree of pain and anxiety they will suffer⁽¹²⁾

Incidence of extravasation is 6.44% in our study. (6.67% in adjuvant and 5.65% in neoadjuvant group). The incidence of extravasation published in the literature ranges between 0.1% and 6.5%⁽⁸⁾

The most frequent complication of peripheral IV infusion is phlebitis which includes pain, erythema, swelling, and palpable thrombosis of the cannulated vein. It which may occur at rates as high as 50%⁽¹³⁾. Singh *R et al*⁽¹⁴⁾, had reported incidence of phlebitis at 59.1% (n=230) amongst their patients requiring peripheral intravenous cannulation. Stephen M. *et al*⁽¹⁵⁾ in 1976 reported the incidence of phlebitis at 31%. In a multicentre epidemiological study of the risks associated with peripheral venous catheters, Tager *et al*⁽¹⁶⁾, found an incidence of phlebitis of only 2.5% among 5161 short term IV catheters. Discrepancy between the incidence rate they observed and that reported by other groups could have been due to the difficulty of standardizing diagnosis among the large number of participating practitioners. The Intravenous Nurses Society established guidelines in 1990 that stated that an acceptable incidence of peripheral vein infusion thrombophlebitis should be 5% or less. This rate exceeds in almost all published studies⁽¹⁷⁾.

Incidence of induration and alteration of colour is present in significant number of cases in 7.16% and 6.98% respectively in patients receiving peripheral intravenous chemotherapy. Yeoh *et al*⁽¹⁸⁾ noted local induration in 7.3% and erythema in 21.1% of their study populations while Martins *et al*⁽⁸⁾, found induration in 3.2% of neoadjuvant and 2.9% of adjuvant cases whereas altered skin colour in 8.3% of adjuvant and 8% of neoadjuvant group. Marshall-McKenaa⁽⁹⁾ *et al* vein discolouration was present in 14 patients (12.72%) out of a total of 110 patients

Following peripheral intravenous chemotherapy cycles, Tissue damage i.e. cellulitis and ulcer occurred in 3.76% cases (4.14% in adjuvant and 2.42% in neoadjuvant groups) and 2.68% cases (2.53% in adjuvant and 3.23% in neoadjuvant groups) which is a significant number. On the basis of the published literature, the progression rate to ulceration in anthracycline extravasations (non-biopsy proven) ranges from 25% to 50%⁽¹⁹⁾

In the study, CEF (cyclophosphamide, epirubicin, and fluorouracil) and PE (paclitaxel, epirubicin) were the most preferred chemotherapy regimen. This findings correlate with facts established from various studies tack et al⁽²⁰⁾, Laurentiis et al⁽²¹⁾. Infusion of regimen containing vesicant compounds should be done by specialised and experienced staff and treatment protocols should be well defined for them.

Contralateral limb must be used for IV access to give peripheral intravenous chemotherapy in carcinoma breast patients for protection of skin (e.g., keep skin clean and dry; avoid punctures such as blood draws, injections, or intravenous infusions no BP, no tourniquets) after breast surgery with axillary dissection to prevent lymphedema over the same side⁽²²⁾. However, these recommendations and guidelines are not evidence based⁽²³⁾. Application of IV cannula on ipsilateral i.e. on the same side of carcinoma breast in adjuvant patients is associated with significantly more incidence of local complication. patients who have undergone radical mastectomy, axillary surgery, or lymph node dissection may have impaired circulation in a particular limb which reduces venous flow and may allow intravenous solutions to pool and leak out⁽²⁴⁾. In neoadjuvant group there was no difference in the occurrence of complications on contralateral or ipsilateral application of IV access in relation to side of breast cancer. IV cannula application on ipsilateral site is associated with 2.08 times (RR=2.08) more chances of local complications following peripheral intravenous chemotherapy. No. 22 Gauge IV cannula must be preferred for peripheral intravenous chemotherapy. Chemotherapy infusion after wide bore IV cannula are associated with more incidence of local complications. Professionals have also looked at the calibre of the device in this scenario, as smaller-calibre devices reduce vascular trauma during the puncture procedure and, if smaller than the vessel calibre, facilitates blood circulation around the device, helping with the hemodilution of the medication⁽²⁵⁾. Singh R et al⁽¹⁴⁾ also found that increased incidence rates of infusion related phlebitis

were associated with small catheter size (20 gauge). However, these studies are in contrast to Holland et al⁽²⁶⁾ who found that gauge of cannula had no influence on the rate of complications.

IV cannula over dorsum of hand should be preferred as it had fewer complications according to the study. Holland et al⁽²⁶⁾ found that the dorsum of the hand was the site with the least number of complications. In both adjuvant and neoadjuvant groups, local complications were common when IV cannula was placed crossing the wrist joint. The most appropriate site is considered to be the forearm. However, it has to be accepted that this is not always going to be an available area. Near Joints area is most commonly implicated in extravasation injuries⁽²⁷⁾. IV cannulation over the wrist have 1.57 times (RR=1.57) more risk of developing local complications as compared to other sites in our study.

If multiple puncture attempts are taken to secure the cannula in the vein, the bevel of the needle can puncture the vein wall during repeated venipuncture, holes remains in the vein wall in the proximity of the venous pricks, allowing drug to escape into the tissue whilst the lumen of the needle may still remain in the blood vessel and allow adequate blood return⁽²⁸⁾. Incidence of local complications in cases following multiple attempts to secure IV cannula is statistically more common compared to those with single prick IV cannulation. Multiple puncture attempts to secure IV cannula is associated with 1.57 times (RR=1.57) more chance of developing local complications following peripheral intravenous chemotherapy.

CONCLUSION

This statement describes the suffering of the patients during a chemotherapy treatment in its complete sense. Utmost care should be taken during chemotherapy infusion. Only trained and specialized staff should be allowed for chemotherapy infusion. The results show that the whole process of chemotherapy, from selection of site for IV access, preparation of drug until end of infusion should be documented at each cycle. Before start of any chemotherapy the patient should be psychologically and emotionally counselled and taken into full confidence. Patient should be made aware of possible complications occurring due to chemotherapy. Maintenance of records is essential for critically evaluating the precision of the complete procedure of chemotherapy infusion and preventing

the occurrence of adverse venous complications. Vigorous monitoring of patient with repeated and frequent examination of site of chemotherapy cannulisation must be done till end of chemotherapy and all observations should be recorded. Should there be any complications, timely intervention with proper treatment guidelines for individual drugs and regimen must be done. Precaution, and care during peripheral intravenous chemotherapy can prevent development of local complications and remove the need for surgical intervention for management of the complications.

More multicentre studies are required to create a data base of venous damage occurring following intravenous peripheral chemotherapy and to formulate standard guidelines and protocols to reduce the rate of complications. It will help to formulate standard guidelines and protocol to help reduce local complications due to peripheral intravenous chemotherapy. Ultimately, it will lead to decrease in development of local surgical conditions requiring less surgical intervention following peripheral intravenous chemotherapy and thus, reducing the additional hospital stay, decrease cost of treatment and removing the hindrance for cancer treatment. This will help to avoid the additional physical, emotional and psychological trauma in already stressed cancer patients.

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