Editorial

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Regional anaesthesia in breast cancer: Benefits beyond pain

Breast cancer is increasingly becoming the most common cancer among females in India. It accounts for around 25%–32% of all female cancers in India as per the National Cancer Registry.[1] Advances in oncology have led to effective treatment of breast cancers. Availability of better chemotherapeutic agents has made breast surgery possible for tumours that were previously considered inoperable.

WHY DO WE WORRY WHEN EFFECTIVE CANCER THERAPY IS AVAILABLE FOR BREAST CANCER?

As onco-anaesthesiologists, we need to follow the technique that would be safest and optimal not only with regard to immediate perioperative outcomes but also for long-term outcomes. One of the important determinants of long-term outcome is cancer recurrence.[2] In spite of all the advancements in surgical, medical and radiation oncology, the risk of recurrence and metastases persists for breast cancer. The perioperative period is characterised by the presence of circulating tumour cells and minimal residual disease, which may lead to tumour recurrence. Many factors in the perioperative period have been implicated in the increased risk of recurrence. These factors include anaesthetic technique, use of opioids, inadequate pain control, hypoxia, hyperglycaemia, hypotension, allogeneic blood transfusion and inadvertent intraoperative hypothermia.[2] The surgical intervention itself is responsible for systemic shedding of tumour cells and thus increasing the risk of metastases.

Pain may influence body homeostasis and cancer progression by pain-related immune suppression. This occurs due to neuroendocrine responses such as triggering of the sympathetic nervous system and hypothalamic-pituitary-adrenal axis and increase in the immunosuppressive β-endorphin concentration in the peripheral immune system.[3] A systematic review and meta-analysis of experimental studies showed that the provision of effective analgesia reduces both the number and incidence of metastases in experimental cancer models.[4]

ROLE OF REGIONAL ANAESTHESIA IN BREAST SURGERY OUTCOME

Breast cancer requires various surgical interventions like lumpectomy or mastectomy along with axillary lymph node clearance. General anaesthesia is the conventional, most frequently used anaesthetic technique. Various regional anaesthetic techniques interventions have also been used for breast surgeries; these include local wound infiltration, thoracic epidural anaesthesia, thoracic paravertebral block, thoracic spinal anaesthesia, and more recently, ultrasound-guided interfascial plane blocks such as pectoral nerve (PECS) blocks type 1 and 2 and the serratus plane block (SPB). Regional anaesthesia provides effective anaesthesia and analgesia in the perioperative setting. Although the beneficial analgesic effect of regional block is well known, data are emerging for the other potentially beneficial effects of regional anaesthesia and analgesia on other perioperative outcomes.[2] These include decreased need for opioids for controlling post-operative pain, decreased post-operative nausea vomiting (PONV), fewer post-operative pulmonary complications and decreased duration of post-anaesthesia care unit stay.[5] More exciting are the potential benefits of regional anaesthesia and analgesia on long-term oncological outcomes. Regional anaesthesia may reduce cancer progression by attenuation of the surgical stress response, better analgesia, and reduced opioid usage, and by the direct protective action of local anaesthetics

on cancer cells migration.[6] Through robust data are not available for making any conclusive statement or recommendations for these beneficial effects and making it an integral part of the anaesthesia protocol, regional anaesthesia and analgesia should be considered for breast onco-surgical procedures.

The complex interaction between inflammation, immunosuppression, hypothermia, and angiogenesis, along with an increased adrenergic state can facilitate the growth of the minimal residual disease and promote the seeding of circulating tumour cells. Hence, different investigators have suggested that any intervention that could modulate all these factors would have a major impact on cancer progression and metastasis. Regional anaesthesia is considered protective for cancer recurrence by its indirect and direct antiproliferative effects.[6] The former are related to suppression of the neuroendocrine stress response, maintained NK cell activity, increased protective cytokines, lesser regulatory T-cells and Th2 cells and reduced C-reactive protein levels.[7] The alteration in the immune response in the perioperative period has been correlated with tumour metastases. The prevention of cancer recurrence is mediated by NKcells, D4+Th1, CD8+CTL and cytokines including interleukin-12 (IL-12), interferon-α/β, interferon-γ and tumour necrosis factor- α (TNF-α).[6] Pro-inflammatory mediators such as IL-6, TNF-α, IL-1β and prostaglandinE2 promote tumour growth. Regional blocks preserve immune function by attenuating the surgical stress response and diminishing the need for opioids. Among the earliest published papers is a retrospective analysis on breast cancer patients which found that patients operated under paravertebral anaesthesia and analgesia combined with general anaesthesia had a lower incidence of breast cancer recurrence than patients who received general anaesthesia alone for mastectomy and axillary clearance. The authors proposed that it could be due to the beneficial effect of the regional block along with the opioid sparing effect.[8]

Opioids and volatile anaesthetics have been associated with immunosuppression and thus the risk of tumour recurrence.[9-11] Regional anaesthesia may be beneficial because of its opioid and volatile anaesthetics sparing effect. Opioids promote tumour growth and metastasis by modulation of cellular and humoral responses leading to immunosuppression, direct action on tumour cells and immune or endothelial cells and the activation of neuroendocrine-mediated stress response leading to the progression of metastasis and angiogenesis. However, there are conflicting data with regard to evidence of implication of opioids with increased risk and number of metastases.[4,6] Volatile anaesthetics have been reported to induce carcinogenic effects through impact on hypoxia-inducible factors and insulin-like growth factors, both of which are potentiated by the use of volatile anaesthetics.[12,13] Sevoflurane induces cell motility and invasion by reduction of matrix metalloproteinase (MMP)-2 and MMP-9126, and xenon inhibited migration in breast adenocarcinoma acells.[14] However, conflicting data exist about volatile anaesthetics as well.

The systemic effects of local anaesthetics agents used for regional blocks have been documented to be cancer protective by inhibition of TNF-α–induced Srcactivation and intercellular adhesion molecule-1 phosphorylation, inhibition of the epidermal growth factor receptor (EGFR) pathway, antiproliferation of mesenchymal stem cells and blockade of the α-subunit of voltage-gated sodium channels.[15-18] Both lidocaine and bupivacaine in clinically relevant concentrations have been shown to induce apoptosis in human breast cancer cells, and therefore may be ideal infiltration anaesthetics in breast cancer surgery.[19] The local anaesthetics *per se* provide analgesia by their systemic effect as well and thus have an opioid-sparing effect. These overall benefits may be protective for cancer recurrence.

OTHER BENEFICIAL OUTCOMES

The other beneficial effect of regional analgesia appears to be reduced occurrence of PONV. This is related to better analgesia and opioids/inhalational anaesthetics sparing effect by regional blocks.[20,21] One of the factors for the occurrence of persistent breast cancer pain syndrome and phantom breast is the suboptimal management of perioperative pain.[20,22] By providing adequate analgesia by regional anaesthesia during breast surgery, these chronic breast pain syndromes appear to be ameliorated.[23,24] A meta-analysis and Cochrane review for persistent pain after breast surgeries revealed that pre-operative regional blocks are effective for reducing chronic pain after breast cancer surgery.[25,26] In view of all these benefits, regional techniques for breast surgery would make breast surgeries feasible for ambulatory setup.[27-29]

QUEST FOR CONCLUSIVE EVIDENCE!

The current evidence on the benefit of regional anaesthesia and analgesia on long-term oncological outcomes is not conclusive. There are no data from randomized trials. Most of the data at present are from retrospective studies or unplanned secondary analyses of randomised trials. There are no comparative studies for efficacy of anaesthetic techniques and drugs with standardised outcomes. There is heterogeneity with regard to cancer type and stages.[30,31] As onco-anaesthesiologists, we need to have more robust well conducted prospective randomized trials for studying the impact of regional technique on tumour recurrence and metastases in breast cancer surgeries. Since many of the newer blocks have been recently introduced, the data is scarce and any recommendations for the same may not be feasible.

To conclude, preservation of perioperative homeostasis using a balanced anaesthesia inclusive of regional block may be protective for cancer recurrence along with other beneficial effects. At present, it would be difficult to recommend a specific anaesthetic or analgesic technique for preventing cancer recurrence. However, based on existing literature, the perioperative management of onco-surgical breast cancer patients should receive comprehensive and targeted management for physiological homeostasis. This could be achieved by incorporating regional anaesthesia technique as a part of balanced anaesthesia for breast surgeries. It is reasonable to minimize the use of volatile anaesthetics and opioids using regional anaesthesia. Further well designed high-quality studies are warranted to assess the impact of regional anaesthesia and analgesia on breast cancer surgery not only with post-operative pain as the primary outcome but also on other important outcomes such as chronic pain, phantom breast pain, nausea and vomiting. This would probably help in formulating a perioperative care plan for patients undergoing breast cancer surgeries. Ongoing randomized controlled trials to determine the impact of regional anaesthesia on oncological outcomes will provide definitive guidance in future.

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