of antidepressants on the brain. This would control for an important confounder.

Other points of concern pertain to not specifying the age of onset and duration of illness, which may have an impact on the neurobiological changes at baseline or with treatment. Also, assessment of intelligence quotient is important in cognitive behavioural therapy. The authors mentioned excluding individuals with intellectual disability but it is difficult to know from the article which tests were applied to ascertain the intelligence quotient.

Considering the various strengths and limitations, it is apparent that the study has opened gates to the possibility of sustained neurobiological effects of MBCT in patients with panic disorder, which may be adapted to subsequent research and incorporated into clinical practice in India as the acceptance for non-pharmacological measures for psychiatric illnesses is high.

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Peritumoural infiltration of lidocaine during breast cancer surgery

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SUMMARY

Events during surgery are seldom taken into account in the natural history of breast cancer. There is evidence of dissemination of tumour cells leading to metastases during surgical removal of the tumour. It might also stimulate growth of pre-existing micrometastases, leading to an early increase in metastatic disease. Surgery-induced hypoxia may activate pro-metastatic pathways through voltage-gated sodium (Na) channels.

Local anaesthetics inhibit voltage-gated Na channels and thus inhibit cellular proliferation and facilitate cell-to-cell adhesion, thus reducing metastatic capability of the primary tumour. They are also known to modulate non-receptor tyrosine-protein (Src) kinases.

A Cochrane review concluded inadequate evidence to support the use of regional anaesthesia agents[1] and therefore an open-labelled, randomized controlled trial to assess the effect of infiltration of local anaesthetic (LA) around a primary breast cancer before extirpative surgery (BCS [breast conservation surgery]/modified radical mastectomy [MRM]) in women with early breast cancer (EBC) was conducted.

Patients with operable breast cancer with clinical N0/N1 nodal status with no evidence of distant metastasis and ECOG (Eastern Cooperative Oncology Group) performance status score of 0 were included. Those who had had a prior incisional or excisional biopsy, had received neoadjuvant chemotherapy (NACT) or hormone therapy, or had benign disease were excluded. The patients were stratified by treatment centre, tumour size and menopausal status.

Patients allocated to the LA arm were administered 0.5% lidocaine around all six surfaces (superior, inferior, anterior, posterior, medial, lateral) of the primary tumour after induction. The planned surgical procedure (MRM/BCS) was initiated 7–10 minutes after administration of lidocaine. Postoperatively, all patients received standard adjuvant therapy. Systemic chemotherapy was given using six cycles of anthracycline in node-negative and four cycles of anthracycline followed by 12 weeks of taxane therapy in node-positive disease. Her-2-neu-positive patients received adjuvant trastuzumab. Patients who underwent BCS and those who had MRM with tumour size ≥5 cm and/or node-positive disease were administered standard postoperative radiotherapy. Patients with hormone receptor-positive status were planned for tamoxifen if premenopausal or aromatase inhibitor if postmenopausal, for at least 5 years. All patients were followed up at 6-month intervals with history and clinical examination. Mammography of the contralateral and/or remnant breast was done every 18–24 months. Evaluation for distant metastatic disease was done in symptomatic patients or in those with loco-regional recurrence.

The primary end-point of the study was disease-free survival (DFS). It was defined as the time interval between randomization and local/regional/distant metastases or contralateral breast cancer or death due to any cause whichever occurred first. The secondary end-point was overall survival (OS) defined as the time interval between randomization and death due to any cause.

Locoregional recurrence was defined as re-appearance of index cancer in the breast/chest wall/regional nodes as the first event while death without recurrence/distant recurrence/occurrence of a non-breast second cancer were defined as competing events if they occurred first.

Distant recurrence was defined as occurrence of distant metastases as the first event while death without recurrence/locoregional recurrence/occurrence of non-breast second cancer were defined as competing events if they took place first.

DFS and OS were estimated using the Kaplan–Meier method and compared between the LA and non-LA arm using the log rank test.

At a median follow-up of 68 months (range 0.5–72 months), the 5-year DFS rate was 86.6% in the LA arm versus 82.6% in the non-LA arm (HR 0.74, p=0.02).

Subgroup analyses of DFS revealed a similar effect of the use of LA in all subgroups.

There was not much difference in the effect of LA in patients who underwent BCS (HR 0.703; 95% CI 0.496–0.996) or mastectomy (HR 0.73; 95% CI 0.50–0.104). There was no difference in Her-2-positive patients who received (DFS HR 0.69; 95% CI 0.25–1.94) or did not receive (DFS HR 0.57; 95% CI 0.30–1.06) Her-2 targeted therapy. The 5-year OS was 90.1% in the LA arm versus 86.4% in the non-LA arm (HR 0.71; 95% CI 0.53–0.94). Subgroup analyses suggested a similar impact of LA in different subgroups.

The competing risk analyses showed that the use of LA reduced locoregional recurrences with a 5-year cumulative incidence of 3.2% in the LA arm and 4.1% in the non-LA arm (sub-distribution HR 0.69; 95% CI 0.42–1.13). It showed reduction in distant recurrences with 5-year cumulative distant recurrence of 8.1% in the LA arm and 10.9% in the non-LA arm (sub-distribution HR 0.74; 95% CI 0.54–1.01). No adverse events due to injection of lidocaine were reported.

Thus, the results of the study suggested statistically and clinically significant improvements in DFS and OS in patients with EBC with relative risk (RR) reduction of 26% and 29%, respectively, in patients with peritumoural infiltration of LA compared to non-administration of LA during surgery.

The adequate sample size and multicentre participation suggests generalizability of the results. The intervention was easily implementable as a one-time procedure and was easily available and cheap. The lack of placebo controls and non-blinding of the patients/investigators were limitations of the study.

COMMENT

The present study shows a remarkable 4% improvement in OS with the use of peritumoural infiltration of lidocaine. However, this raises several questions.

This multicentre trial involved 11 institutions. However, the number of patients contributed by each centre are not given in a tabular form, which would have aided the readers in generalizing these observations to their own settings. This is important to know as Tata Memorial Centre, Mumbai is an apex quaternary referral centre for cancer care in India. The generalizability of the study would be weakened if there was uneven recruitment from the apex cancer centre.

The authors state that infiltration of lidocaine was done around all six surfaces of the tumour. However, no imaging was done to confirm the completeness of infiltration on all sides. The technical aspects of injecting large quantity of fluid around the tumour poses certain surgical challenges. The presence of fluid all around the tumour can interfere with accurate palpation of the tumour, reduce the accuracy of palpation-guided surgery and thus may affect the margin status and volume of tissue removed. In addition, monopolar electrocautery or other energy devices do not work with full efficiency in the presence of excessive fluid within tissues because of dissipation of energy in different directions, thus prolonging surgical time and causing more lateral damage. Moreover, in screen-detected impalpable lesions, which is the commonest presentation of EBC in the West, infiltration of the drug all around the tumour will be a challenge and may need to be done under image guidance.

The molecular basis of the remarkable outcome of this study is hypothesized as alteration of gene expression in the tumour and subsequent metastasis.[2] However, all of these happening within 60 minutes or so (average operating time of mastectomy or BCS) appears improbable. In addition, Turnbull's 'no touch technique' of ligation of inferior mesenteric artery first to prevent tumour dissemination in colorectal cancer,[3,4] addressing the axilla 'first' before mastectomy or BCS to prevent tumour dissemination and use of perioperative chemotherapy[5] in breast cancer to destroy tumour cells dislodged during surgery have not been shown to alter outcomes. Also, routine massage of the breast while performing sentinel node biopsy, which should potentially disseminate tumour cells, has not been shown to be associated with any adverse outcome in breast cancer.

Lastly, this study is akin to a drug trial. A new or 're-purposed' drug needs to go through different phases of clinical drug trial design, viz. phases 1, 2 and 3. Not having conducted a pilot study (phase 2 trial) to show the beneficial effects of peritumoural lidocaine administration and not having a placebo arm in this study, as the authors themselves stated, will be a major hindrance for surgeons the world over to adopt this in routine practice.

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