Human & Veterinary Medicine
International Journal of the Bioflux Society HVM

OPEN ACCESS
Research Article

The use of regional anaesthetic blocks and local wound anaesthetic injection for the management of postoperative pain in breast cancer surgery - prospective study

[1]Ana M. Văduva, [2,3]Călin Ionescu, [4]Cornel Cheregi, [3]Mihai S. Mihalcea, Mihai Ș. Mureșan

[1] Obstetrics and Gynaecology Department, "Dominic Stanca" Gynaecology Clinic, Cluj-Napoca, Romania; [2] Surgery Department – Cluj-Napoca Municipal Hospital, Cluj-Napoca, Romania; [3] VIIth Surgical Department, Vth Surgical Clinic – "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; [4] Surgery Department – Oradea Military Hospital, Oradea, Romania.

Abstract. Introduction. Breast cancer is one of the most frequent diagnosed cancers in women worldwide. Even though the extent of radical surgery has dropped, in the past decades, the percentage of mastectomies performed is still high. Immediate postoperative pain is correlated to the prevalence of chronic reported pain. NSAIDs are considered not enough for the management of subjective local pain reported by breast cancer patients. For this matter, regional anaesthetic blocks, wound anaesthetic injections or a combinations of thereof, have provided successful and promising results. The aim of this study was to assess and compare the impact of postoperative pain on the quality of life in breast cancer surgery, both in patients who have undergone regional (pectoral, paravertebral or wound infiltration) anaesthetic block and in those who have not been given local anaesthetic for pain control, and, further on, to compare the subjective perceived pain in the same group of patients. Patients and Methods. We have prospectively selected a preliminary cohort of 20 breast cancer patients irrespective of neoadjuvant chemotherapy, operated in a tertiary Surgical facility by a single surgical team, either via a conservative or via a radical approach. All relevant demographics and cancer-related data was recorded. We have reported and compared the pain scores (McGil and Present Pain Intensity-PPI) in relation to the surgical approach. Results. The average age of patients was 53.75 ± 12.51 years, with more patients coming from a rural setting, bearing a right upper outer quadrant tumour (45%), being subjected to radical surgery (55%), with more than half of the patients without any neoadjuvant treatment. In the current study, 65% of the patients received some sort of regional or local analgesia as adjuvant to usual NSAIDs treatment. Pain reported at 2 months (McGill score) versus pain reported at 6 months postoperatively (PPI score) revealed a decrease both for patients treated with conservative and radical surgery ($p<0.001$, $p<0.001$). Conclusions. Multidisciplinary pain management approaches should be used for every surgical cancer patient. Postoperative pain risk stratification and evaluation should be adapted to each individual case. Regional analgesia approaches seem to offer better quality of life related to perceived pain.

Key Words: breast cancer, regional blocks, wound anaesthetic infiltration, McGill

Copyright: This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Corresponding Author: C. Cheregi, email: cornel.cheregi@yahoo.com

Introduction

Breast cancer is considered the most common malignancy in women not only at an international level, but also in Romania, with most of the patients requiring surgical treatment of the primary tumour consisting in tumour excision (either via a wide local excision or mastectomy) along with axillary node dissection and assessment of lymph nodes at this level. Approximately 40% of these patients will experience pain with a high degree of intensity immediately in the postoperative setting, thus demonstrating that usual NSAIDs medication is not enough. Moreover, acute pain that occurs after breast surgery is considered the main risk factor in the onset of persistent chronic pain, with a negative impact on the quality of life of patients diagnosed with this type of malignancy (Bray et al 2018; Gärtner et al 2009; Poleshuck et al 2006).

Concerning the management of postoperative pain in breast surgery, various regional anaesthesia techniques are used, such as: paravertebral block, epidural block, intercostal block, pectoral block, but also local anaesthetic infiltrations into the wound. Although the paravertebral block is most often used in addition to non-volatile anaesthesia and postoperative pain relief, patients with modified radical mastectomy (MRM) often have pain in the armpit and ipsilateral upper limb because this block does not achieve sufficient analgesia in the pectoralis muscles (Gärtner et al 2009; Wahba & Kamal, 2014)

Assessing the intensity and severity of pain experienced by the patient is considered an essential component of proper pain management, but it must be undertaken taking into account both the

qualitative assessment of pain and the impact on the psychological and physical function(Herr et al 2004).
The aim of this study is to assess and compare the impact of postoperative pain on the quality of life in breast cancer surgery, both in patients who have undergone regional (pectoral, paravertebral or wound infiltration) anaesthetic block and in those who have not been given local anaesthetic for pain control, and, further on, to compare subjective perceived pain in between patients undergoing either breast conserving or radical surgeries.

Material and methods

General structure of the study

The current study is an observational, analytical, prospective and longitudinal study. The data collection included the period May 2019 - November 2019, when we collected data on female patients admitted to the Surgery Department of Cluj-Napoca Municipal Hospital, Cluj-Napoca, Romania, who underwent one of the surgical techniques for the treatment of breast cancer (either breast conserving surgery – BCS, or modified radical mastectomy – MRM). Following the inclusion and exclusion criteria applied in this study, out of 87 female patients initially eligible for inclusion in the study, based on the application of the criteria, we selected for analysis a number of 20 patients with breast cancer, undergoing multidisciplinary surgical management, by a single team consisting of a primary surgeon, a secondary surgeon, an anaesthesiologist and a ward nurse. The study has been approved by the Head of the Surgery Department, after prior revision by the institution's Ethics' Committee (Reg. No. 1/2019).

Criteria for inclusion of patients in the study

- Patients with breast cancer regardless of clinical staging, primarily operated or after neoadjuvant chemotherapy;
- Patients who received a regional anaesthetic block (either using Ropivacaine 0.25% or Bupivacaine 0.25%);
- Patients who have not had a regional anaesthetic block;
- Patients who received local anaesthetic wound infiltration (WI - either using Ropivacaine 0.25% or Bupivacaine 0.25%);
- Patients with complete clinical charts;
- Patients with known last follow-up date (postoperative follow-up of at least 6 months);
- Patients who have expressed in writing/by telephone their informed consent to participate in the study.

Exclusion criteria applied to patients in the study

- Patients with non-oncological breast pathology;
- Patients who were lost to follow-up after neoadjuvant therapy;
- Patients with unknown last follow-up date or postoperative follow-up less than 6 months;
- Patients who did not express in writing/by telephone their informed consent to participate in the study;

The following were NOT excluded from the study:

- Patients who were diagnosed in another centre and requested specialized surgical treatment at Cluj-Napoca Municipal Hospital;
- Patients receiving other types of neoadjuvant therapy, excluding chemotherapy (i.e hormone receptor inhibition)

Data collection and analysis methodology

Patient data was entered into a worksheet and then into a Microsoft Excel ® 2010 database. The parameters followed in the study were: diagnosis, personal identification number, age, background, ontologically relevant personal history, pain score according to the abbreviated form of the McGill short-form questionnaire (Melzack 1987; Turk D & Melzack R 2011) (postoperative pain perceived at 2 months post-surgery) (Table 1), present pain experienced (PPI - Present Pain Intensity – at 6 months post-surgery (Fig.2) (Melzack 1987), surgical technique used, date of surgery, status of neoadjuvant treatment, type of local anaesthetic used for the anaesthetic block, anaesthetic technique used.

Pain Intensity →	None	Mild	Moderate	Severe
Pain character ↓				
Throbbing	0)___	1)___	2)___	3)___
Shooting	0)___	1)___	2)___	3)___
Stabbing	0)___	1)___	2)___	3)___
Sharp	0)___	1)___	2)___	3)___
Cramping	0)___	1)___	2)___	3)___
Gnawing	0)___	1)___	2)___	3)___
Hot-Burning	0)___	1)___	2)___	3)___
Aching	0)___	1)___	2)___	3)___
Heavy	0)___	1)___	2)___	3)___
Tender	0)___	1)___	2)___	3)___
Splitting	0)___	1)___	2)___	3)___
Tiring/Exhausting	0)___	1)___	2)___	3)___
Sickening	0)___	1)___	2)___	3)___
Fearful	0)___	1)___	2)___	3)___
Punishing/Cruel	0)___	1)___	2)___	3)___

Fig. 1. McGill short-form questionnaire (postoperative pain perceived at 2 months post-surgery), Adapted from(Melzack, 1987; Turk D & Melzack R 2011)

The data regarding the perceived pain (at 2 months after surgery - by assessment using the McGill score, respectively, the present pain intensity - evaluated by the PPI scale), were obtained by contacting the patients by telephone and recording the answers offered by them.
The reporting of descriptive statistical data was done using the same software, for quantitative variables (mean +/- standard deviation, with 95% confidence interval (CI) and histograms), and for qualitative variables, contingency tables and pie charts were used. Analytical statistics (comparison of perceived pain

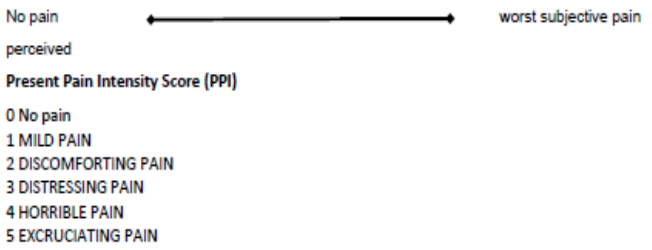

Fig. 2. Present pain experienced (PPI - Present Pain Intensity – at 6 months post-surgery) Adapted from Melzack (1987)

between types of surgery performed, between types of loco-regional anaesthesia performed, and between types of perceived pain - at two months after surgery, respectively at the time of the telephone interview) were analysed using the t-Student test: two-sided, assuming unequal variances, considering a value of $p < 0.05$ statistically significant.

Results

Of the 20 female patients included in the study sample, 11 came from rural areas and 9 from urban areas, with a higher share of those from rural areas. The average age of patients was 53.75 ± 12.51 years (95% CI: 27-78 years). Following the age distribution of patients at the time of admission, a peak can be noticed at the age range 43-59 years.

Depending on the location of the tumour, an attempt was made to find the location in a dominant quadrant of the breast, irrespective of side of the disease (Fig. 3), noticing a higher frequency at the level of the upper-outer quadrant of the right breast (Fig. 4, Fig. 5).

In relation to the type of surgical procedure performed, more than half (55%) of the patients were subjected to a modified radical mastectomy, 35 % of the patients were subjected to breast conserving surgery and 10 % of the patients underwent bilateral MRM.

The most frequent primary tumour histology was Invasive Ductal Carcinoma (IDC) – found in 80% of the patients, whereas ductal carcinoma in situ (DCIS) and Lobular carcinoma in situ (LCIS), were reported for about 10%, each.

Out of the total number of patients treated by surgery, only 45% of them received neoadjuvant chemotherapy.

Surgical wound infiltration (WI) of local anaesthetic was the approach used for the management of postoperative pain in 45% of the cases; a percent of 35% did not receive neither a pectoral block nor would infiltration, and the rest of 20% received different types pectoral blocks (Type I, II and III).

For patients whose surgical approach was Breast Conserving Surgery (BCS), the postoperative pain management showed no difference between the number of patients receiving usual intravenous NSAIDs and those managed via WI (43% of the cases). A similar situation was noticed for patients that were subjected to modified radical mastectomy (MRM); all patients with bilateral radical mastectomy were managed via WI.

The reported pain score of each patient is obtained using the abbreviated form of the McGill pain scale questionnaire by telephone interview at 2 months after surgery. The score varies between a value of 3 and 12, with a maximum value of 14. The reported present pain intensity score (PPI) is obtained using the same telephone interview, at 6 months postoperatively.

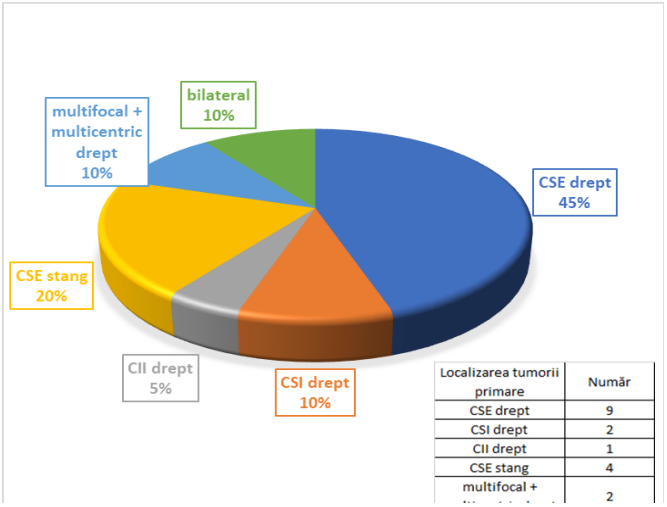

Fig. 3. Location of the primary tumour

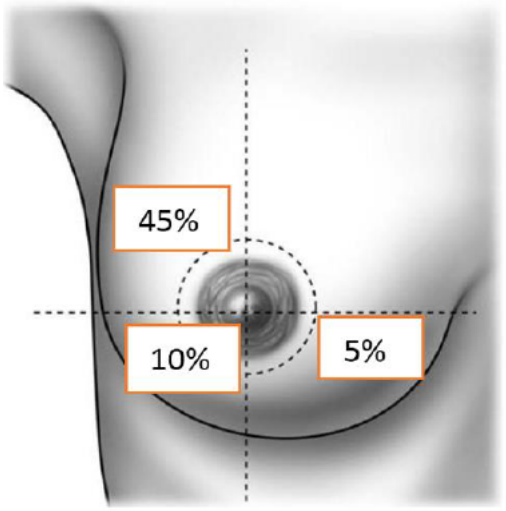

Fig. 4. Location of the primary tumour in the right breast quadrants

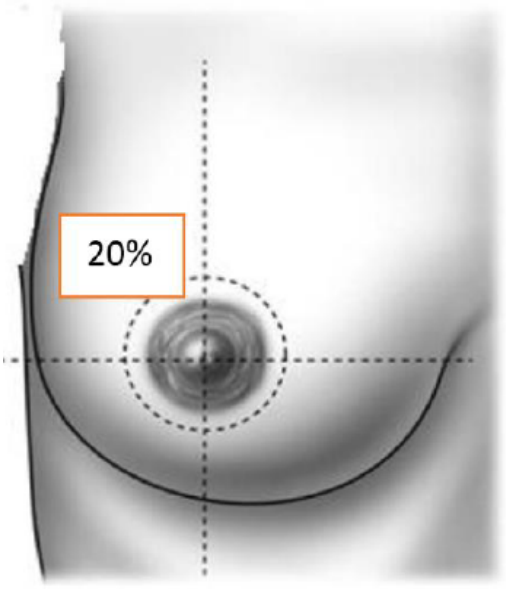

Fig. 5. Location of the primary tumour in the left breast quadrants

The score had a value of 0 for 8 of our patients, the rest varied between 1 and 5.

For patients operated by BCS, comparing the results obtained using the McGill pain scale (2 months after surgery) with the present pain intensity measured by the PPI scale (6 months postoperatively), we noticed a significant decrease in pain ($p = 0.003$).

For the same cohort of patients (BCS), when comparing the McGill pain scale (2 months after surgery) of the patients managed with local WI/PB vs. the scores reported by patients managed solely with usual NSAIDs intravenous analgesia, we did not notice significant differences in pain levels reported subjectively by patients ($p = 0.31$).

On the other hand, the levels reported using the PPI scale for BCS patients, show an improved trend of reported pain, in patients initially receiving local WI vs. those managed solely with usual NSAIDs ($p = 0.047$).

For patients operated by MRM (regardless of the bilateral status of the surgery) when comparing the McGill pain scale (2 months after surgery) with the present pain intensity measured by the PPI scale (6 months postoperatively), we notice an even more significant decrease in pain, as per patients managed by BCS ($p<0.001$).

Furthermore, as per patients operated with BCS, a similar situation was found in MRM when comparing patients, analysing the McGill pain scale (2 months after surgery) of the patients managed with local/regional pain management (WI/PB) vs. pain reported by patients managed solely with usual NSAIDs intravenous analgesia. In this matter, no significant differences in pain reported subjectively by patients was found ($p = 0.27$).

Present pain intensity scores reported subjectively by the PPI scale for patients treated by radical surgery (MRM) show a similar trend in pain perception, regardless of the type of analgesia (WI/PB vs. usual NSAIDs) used, without any statistical significance ($p = 0.45$).

Discussions

This study was performed on a sample of 20 female patients with breast cancer who underwent surgical treatment, who were contacted by telephone two months after discharge to assess their pain using the abbreviated form of the McGill questionnaire; patients were also subsequently interviewed on pain intensity perception, using the PPI scale (6 months after their initial surgery).

One of the limitations of the present study is the small number of patients included in the follow-up period. We have to underline the fact that this was just a preliminary report of a much larger cohort of oncological patients, which were treated with curative intent in a multidisciplinary setting. It is to our best belief that subsequent reports concerning these patients, will be published by our team, thus underlying the importance of either regional or local analgesia as tools in the armamentarium used to improve the quality of life of cancer patients.

The demographics reported by our current study, somehow comes in trend with several other data available in the literature, as per below.

The average age of the patients included in the study at the time of admission was 53.75 years. Thus, our cohort of breast cancer patients, present with an average age of cancer offset, below the average age of diagnostics for breast cancer worldwide, which is 62. The peak incidence of age in this study is the interval situated between 43-59 years, which comes to contrast several other data reported by other studies (Bray et al 2018).

When investigating the site of the primary tumour, the most frequent location was the upper-outer quadrant (UOQ) of the right breast (45%), similar to the data reported by other cohort studies. The second most frequent location was the UOQ of the left breast (20%) (Jatoi et al 2005).

Invasive ductal carcinoma (IDC) of the breast, was the most common reported histological finding concerning the primary tumour (16 cases, 80%), followed by DCIS (10%) and LCIS (10%). Similar data were reported by Feig BW et al, somehow concurring with other cohorts found in other reports, where IDC was reported to be in a percentage of 85% (Feig et al 2015).

Out of the total number of patients, 11 (55%) received neoadjuvant therapy in a different Cancer Centre, elsewhere than the surgical ward were the curative surgery was performed; this facilitated the subsequent BCS approach.

The therapeutic option used for 65% of the cases was MRM, whereas BCS was considered for only 35% of cases (with subsequent adjuvant external beam radiotherapy treatment - EBRT, for the remnant breast). Unfortunately, these percentages remain consistent in the past decade, not only for our surgical team, but also for our region. This can be explained both by the somehow more advanced stage at diagnosis (epidemiological data, not shown in this study) and by the multidisciplinary team decision, when in most of the times, since EBRT is not available for all of the patients, more radical surgery is considered. All of the above reasons still offer a constant trend towards more radical surgeries, compared to conservative ones, in a much higher percentage compared to other results reported in the literature (Bashandy & Abbas, 2015; Bray et al 2018; Campbell et al 2015; Rica et al 2007).

For the management of postoperative pain, regardless of the type of surgery performed, we still see a high trend of the use/overuse of usual postoperative analgesia (NSAIDs, opioids) as sole postoperative pain management tool, for 35% of patients in our study; for the remaining 65%, either PB (5%) or PB and WI (15%), WI alone (45%) were performed. This is somewhat different from the current therapeutic trend (Bashandy & Abbas, 2015; Wahba & Kamal, 2014) where 35% of patients undergo paravertebral block (not performed in our sample), PB, WI or a combination thereof. In our cohort, as the radical interventions had a higher prevalence, we also notice a higher benefit (65%) when judging the reported pain scores for these patients when WI was used.

Several studies have compared the results of subjective pain scores reported when using postoperative pain management (regional blocks +/- WI) either using Bupivacaine 0.25-0.5% or Ropivacaine 0.25-05%, without identifying a significant difference related to either concentration or substance used18-21. For our cohort, Ropivacaine 0.25% was used for all of the cases (irrespective of type of local/regional analgesia performed), thus we consider that our preliminary results would not have been influenced by the use of Bupivacaine 0.5%. Several other authors have described the preference for wound infiltration (WI) with Ropivacaine 0.25%, to the detriment of other local anaesthetics (Albi-Feldzer et al 2013; Rica et al 2007; Vigneau et al 2011).

The statistical analysis of pain reported by McGill score (2 months after surgery) reveals a reduced pain sensation, regardless of the surgery performed, for patients who underwent pain management by WI +/- PB. This is true for both BCS and radical surgery. Paradoxically, this is no longer the case, regardless of the surgery performed and the subsequent re-assessment by the PPI scale.

Pain assessment methods show variations in sensitivity and specificity, depending on the age of patients subjected to surgery. Several other pain assessment tools and scales are widely used, such as: visual analogic scale, numerical scale, visual descriptive scale, Becker's Face Recognition Evaluation (Moller et al 2007). In this study, we used the abbreviated form of the McGill questionnaire, with a superior sensitivity to other methods of pain assessment, as demonstrated in several other studies (Poleshuck et al 2006; Turk & Melzack 2011).

One other important limitation of this study was the lack of investigation of the reported pain, immediately after surgery, on the first day after the procedure, respectively the comparison of these initial reported values with a subsequent re-assessment by telephone interview 2 months after discharge. Other studies report the assessment of pain felt at an interval of 1-10 postoperative days, through standardized questionnaires, with subsequent re-assessment at 30 days(Blanco 2011; Kulhari et al 2016; Wahba & Kamal 2014). The third limitation of this study was the lack of randomization of the type of analgesia used, as well as the comparison with a negative control (placebo) regarding the administered substance. For all patients in our sample, both WI, PB or a combination thereof was performed with Ropivacaine 0.25%.

It is to our best belief that a multidisciplinary approach for pain management using pre/perioperative invasive procedures (PB, WI, vertebral block or a combination thereof) provided by the surgeon, anaesthetist, and ward nurses should be provided whenever possible and feasible. Our preliminary data show promising results in future cohorts of cancer patients, irrespective of the radicality and surgical approach. The large-scale implementation of breast cancer screening methods will be able to help with an early diagnosis and the application of a less radical treatment, with a much-diminished postoperative pain. Assessment of reported pain after breast surgery should be performed in the immediate postoperative period and subsequently monitored at well-established time intervals. Pain assessment questionnaires need to be standardized and uniformly adopted by specialized Surgical Oncology Units, in order to facilitate palpable results comparable to other cohorts of cancer patients. WI/PB/vertebral block or combination thereof are useful, feasible and reproducible methods for the management of early and late postoperative pain, as an alternative to the usual analgesia administered. An increase in the use of these techniques could reduce the use of minor/major analgesics used in the postoperative setting of breast cancer surgery.

Conclusions

Our reported data, reemphasizes the well-known dogma that, breast cancer patients should be assessed, diagnosed and treated in a multidisciplinary centre specializing in this pathology (Breast Unit), thus facilitating post-therapeutic follow-up.

References

Albi-Feldzer A, Mouret-Fourme E E, Hamouda S, Motamed C, Dubois P-Y, Jouanneau L, et al. A Double-blind Randomized Trial of Wound and Intercostal Space Infiltration with Ropivacaine during Breast Cancer Surgery. Anesthesiology 2013;118(2):318–26.

Bashandy GMN, Abbas DN. Pectoral Nerves I and II Blocks in Multimodal Analgesia for Breast Cancer Surgery. Regional Anesthesia and Pain Medicine 2015;40(1):68–74.

Blanco R. The 'pecs block': a novel technique for providing analgesia after breast surgery. Anaesthesia 2011;66(9):847–8.

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians 2018;68(6):394–424.

Campbell I, Cavanagh S, Creighton J, French R, Banerjee S, Kerr E, et al. To infiltrate or not? Acute effects of local anaesthetic in breast surgery. ANZ Journal of Surgery 2015;85(5):353–7.

Feig BW, Berger DH, Fuhrman GM. Anderson surgical oncology handbook. Lippincott Williams & Wilkins; 2015.

Gärtner R, Jensen M-B, Nielsen J, Ewertz M, Kroman N, Kehlet H. Prevalence of and Factors Associated With Persistent Pain Following Breast Cancer Surgery. JAMA 2009;302(18):1985.

Herr KA, Spratt K, Mobily PR, Richardson G. Pain Intensity Assessment in Older Adults. The Clinical Journal of Pain 2004;20(4):207–19.

Jatoi I, Kaufmann M, Petit JY. Atlas of breast surgery. Springer Science & Business Media; 2005.

Kulhari S, Bharti N, Bala I, Arora S, Singh G. Efficacy of pectoral nerve block versus thoracic paravertebral block for postoperative analgesia after radical mastectomy: a randomized controlled trial. British Journal of Anaesthesia 2016;117(3):382–6.

Melzack R. The short-form McGill pain questionnaire. Pain 1987;30(2):191–7.

Moller JF, Nikolajsen L, Rodt SA, Ronning H, Carlsson PS. Thoracic Paravertebral Block for Breast Cancer Surgery: A Randomized Double-Blind Study. Anesthesia & Analgesia 2007;105(6):1848–51.

Poleshuck EL, Katz J, Andrus CH, Hogan LA, Jung BF, Kulick DI, et al. Risk Factors for Chronic Pain Following Breast Cancer Surgery: A Prospective Study. The Journal of Pain 2006;7(9):626–34.

Rica MAI, Norlia A, Rohaizak M, Naqiyah I. Preemptive Ropivacaine Local Anaesthetic Infiltration Versus Postoperative Ropivacaine Wound Infiltration in Mastectomy: Postoperative Pain and Drain Outputs. Asian Journal of Surgery 2007;30(1):34–9.

Turk D, Melzack R. Handbook of pain assessment. New York: Guilford Press; 2011.

Turk D, Melzack R. Handbook of pain assessment. Guilford Press. New York; 2011.

Vigneau A, Salengro A, Berger J, Rouzier R, Barranger E, Marret E, et al. A double blind randomized trial of wound infiltration with ropivacaine after breast cancer surgery with axillary nodes dissection. BMC Anesthesiology 2011;11(1):23.

Wahba SS, Kamal SM. Thoracic paravertebral block versus pectoral nerve block for analgesia after breast surgery. Egyptian Journal of Anaesthesia 2014;30(2):129–35.

Authors

•Ana Maria Văduva, Obstetrics and Gynaecology Department, "Dominic Stanca" Gynaecology Clinic, 55 21 Decembrie Boulevard, Cluj-Napoca, Romania, e-mail: anamariavad@yahoo.com

•Călin Ionescu, Department of Surgery, Cluj-Napoca Municipal Hospital, 11-13 Tăbăcarilor Street, Cluj-Napoca, Romania, VIIth Department of

Surgery, Vth Surgical Clinic, "Iuliu Haţieganu" University of Medicine and Pharmacy, 8 Victor Babses Street, Cluj-Napoca, Romania, email: ionnescu.calincj2002@gmail.com

•Cornel Cheregi, Surgery Department – Oradea Military Hospital, 3 Dunărea Street, Oradea, Romania, e-mail: cornel.cheregi@yahoo.com

•Mihai Sebastian Mihalcea, Department of Surgery, Cluj-Napoca Municipal Hospital, 11-13 Tăbăcarilor Street, Cluj-Napoca, România, e-mail: mihalcea.sebastian@gmail.com

•Mihai Ștefan Mureșan, Department of Surgery, Cluj-Napoca Municipal Hospital, 11-13 Tăbăcarilor Street, Cluj-Napoca, Romania, VIIth Department of Surgery, Vth Surgical Clinic, "Iuliu Haţieganu" University of Medicine and Pharmacy, 8 Victor Babes Street, Cluj-Napoca, Romania, email: mihai.stefan.muresan@gmail.com

Citation	Văduva AM, Ionescu C, Cheregi C, Mihalcea MS, Mureșan MS. The use of regional anaesthetic blocks and local wound anaesthetic injection for the management of postoperative pain in breast cancer surgery - prospective study. HVM Bioflux 2022;14(1):61-66.
Editor	Antonia Macarie
Received	28 January 2022
Accepted	15 March 2022
Published Online	23 March 2022
Funding	None reported
Conflicts/ Competing Interests	None reported