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Research Article

Continuous intravenous infusion of lidocaine for postoperative pain in breast cancer surgery patients. Effect on acute and chronic pain

[1]Elena V. Galoș, [2]Tiberiu F. Tat, [2]Răzvan Popa, [3]Ștefan C. Vesa, [1]Horațiu Vasian, [1]Daniela C. Ionescu, [4]Carmen M. Mihu

[1] Ist Department of Anaesthesiology and Intensive Care, "Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania; [2] "Prof. Dr. Ion Chiricuță" Institute of Oncology, Cluj-Napoca, Romania; [3] Department of Pharmacology, Toxicology and Clinical Pharmacology, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; [4] Department of Histology, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania.

Abstract. Introduction: Postoperative pain after breast cancer surgery influences the length of hospitalisation and its costs, the quality of life and patient reinsertion in the work field. An efficient management of postoperative pain can contribute to increased patient satisfaction and better long-term outcomes after the surgical intervention. Objective: The study aims to assess the ability of continuous low-dose intravenous lidocaine infusion to lower postoperative pain scores, opioid use and their side effects, and to reduce the incidence of chronic pain after breast cancer surgery. Material and Method: This is a randomised controlled study performed in the Institute of Oncology of Cluj-Napoca. The study enrolled 120 patients, 18-80 years old, ASA (American Society of Anesthesiology) physical status class I-III undergoing surgery for primary breast cancer resection, that have signed an informed consent. Patients were randomly assigned to have general anaesthesia associated or not with a continuous intravenous lidocaine infusion from the time of anaesthetic induction (iv bolus of 1.5 mg kg-1) and throughout the surgery (2 mg kg-1h-1), followed by a continuous infusion of 1 mg kg-1h-1 for 24h postoperatively. The first and second outcomes were severity/ the level of postoperative pain assessed by using the visual analogue scale (VAS) and total tramadol dose (mg) required during the first 24 postoperative hours. The third outcome was represented by the development of chronic pain one year after surgery evaluated by using part II of McGill pain questionnaire. Results: Continuous iv lidocaine infusion does not influence postoperative pain scores or the occurrence of chronic pain, but significantly reduces the need for rescue analgesia (p=0.003). Conclusion: Intravenous lidocaine infusion may be a solution for lowering postoperative use of opioids and their side effects in breast cancer surgery.

Key Words: cancer, postoperative pain, lidocaine

Corresponding Author: E V. Galoș: draghiciuelena@yahoo.com

Introduction

Modified radical mastectomy and quadrantectomy are the most frequent variants to mastectomy, performed for the surgical treatment of breast cancer. In 2018 there were 2.088.849 new breast cancer cases worldwide and 626 679 deaths attributable to it with a worldwide incidence of 46.3: 100000 and a mortality rate of 13:100000 (The global cancer observatory 2019). Postoperative acute pain management of patients undergoing this procedure may vary according to local protocoles with the use of multimodal analgesia (a combination of opoid, nonsteroidal anti-inflammatory drugs-NSAIDs, paracetamol etc.) beeing a mainstay. Regional analgesia – through the use of paravertebral block, has emerged in recent years as a technique that can have benefits in terms of lowering factors associated with the progression of the disease (Looney et al 2010) and decreasing the use of opioids also known to have proangiogenic effects (Mao et al 2013). According to some studies chronic pain after breast surgery developes in almost 40% of cases : 39.2% in Turan's study (Turan et al 2014), 38.3% reported by Andersen (Andersen et al 2016), altering the quality of life and delaying full social reinsertion. The role of lidocaine in managing acute postoperative pain and the influence on the development of chronic pain has been studied with conflicting results in breast cancer surgery (Chang et al 2017, De Menezes et al 2014). In this study, we are trying to adress the need for more studies formulated by other reviewers (Kandil et al 2017) and to clarify the role of continuous perioperative low-dose intravenous lidocaine infusion and its impact on acute postoperative pain and the occurrence of chronic pain one year after breast cancer surgery. This study is part of another research (NETosis and angiogenesis expression after intravenous or inhalation anaesthesia with or without i.v. lidocaine for breast cancer surgery: a prospective, randomised trial, published by Bristish Journal of Anaesthesia)

Table 1. Patient's demographic data

Trial Groups	Sevoflurane (S) (n=30)	Sevoflurane + Lidocaine (SL) (n=30)	Propofol TIVA-TCI (P) (n=30)	Propofol TIVA-TCI + Lidocaine (PL) (n=30)
Age (years)	56.1 (32 – 80)	58.34 (42-72)	53.4 (35-77)	57.07 (38-77)
Body-mass index (kg m²)	27 (4.5)	28.5 (4.8)	26.8(5.9)	27.5(5.8)
ASA physical status (n, %)				
ASA I	12 (40)	11 (37)	14 (46)	12 (40)
ASA II	17 (56)	19 (63)	16 (53)	18 (60)
ASA III	1 (3)	0	0	0
Preoperative treatment (n, %)				
Previous chemotherapy	18 (60)	15 (50)	16 (53)	15 (50)
Previous radiation (n, %)	0	0	1 (3)	0
Previous hormonal therapy (n, %)	1 (3)	4 (13)	2 (6)	0
Tumour site (n, %)				
Right	10 (33)	14 (47)	15 (50)	7 (23)
Left	20 (67)	15(50)	15(50)	22(73)
Bilateral	0	1(3)	0	1 (3)
TNM classification				
Pathology stage, tumour (n, %)				
Tx	2 (7)	0	0	0
Tis	2 (7)	1 (3)	0	4 (13)
T0	2 (7)	2 (7)	2 (6)	0
T1	11 (37)	14 (47)	15 (50)	11 (37)
T2	9 (30)	12 (40)	10 (33)	15 (50)
T3	2(7)	1 (3)	2 (6)	0
T4	2 (7)	0	1 (3)	1 (3)
Pathology stage, nodes (n, %)				
Nx	2 (7)	1 (3)	0	4 (13)
N0	14 (47)	14 (47)	18 (60)	12 (40)
N1	7 (23)	6 (20)	6 (20)	10 (33)
N2	6 (20)	7 (23)	5 (16)	6 (20)
N3	1 (3)	2 (7)	1 (3)	0
Pathology stage, metastasis (n, %)				
Mx	23 (76)	20 (67)	25 (83)	25 (83)
M0	7 (23)	9 (30)	4 (13)	5 (17)
M1	0	1 (3)	1 (3)	0

aimed to clarify the role of anaesthesia type on factors that can contribute to tumour progression and metastasis.

Methods

The study was registered with ClinicalTrials.gov (NCT02839668) after obtaining Ethics committee Approval (No 54/14.03.2016). We enrolled 120 ASA I-III class physical status patients, aged 18-80 years of age that were undergoing surgery for primary resection of breast cancer, without known disseminated disease before the surgical intervention, in the setting of Prof. Dr. I Chiricuță Institute of Oncology of Cluj-Napoca, Romania. Exclusion criteria consisted in patient's refusal to participate, incapacity of understanding study protocol or giving informed consent, any allergy to substances used in the study, neuropsichyatric diseases that rendered the patient unable to give informed consent, presence of chronic inflammatory disease, diabetes, ischemic cardiovascular disease, endometriosis and peripheral vascular disease. After obtaining informed consent based on the Helsinki declaration, patients were computer-randomised in an 1:1:1:1 ratio to one of the four anaesthesya type groups: Sevoflurane anaesthesia alone (S); Sevoflurane anaesthesia plus IV(intravenous) lidocaine (SL), Propofol Target-Controlled Total Intravenous anaesthesia (TIVA-TCI) (P), and Propofol TIVA-TCI anaesthesia plus IV lidocaine (PL). The allocation to either group was performed just before surgery (see Table 1 and Figure 1).

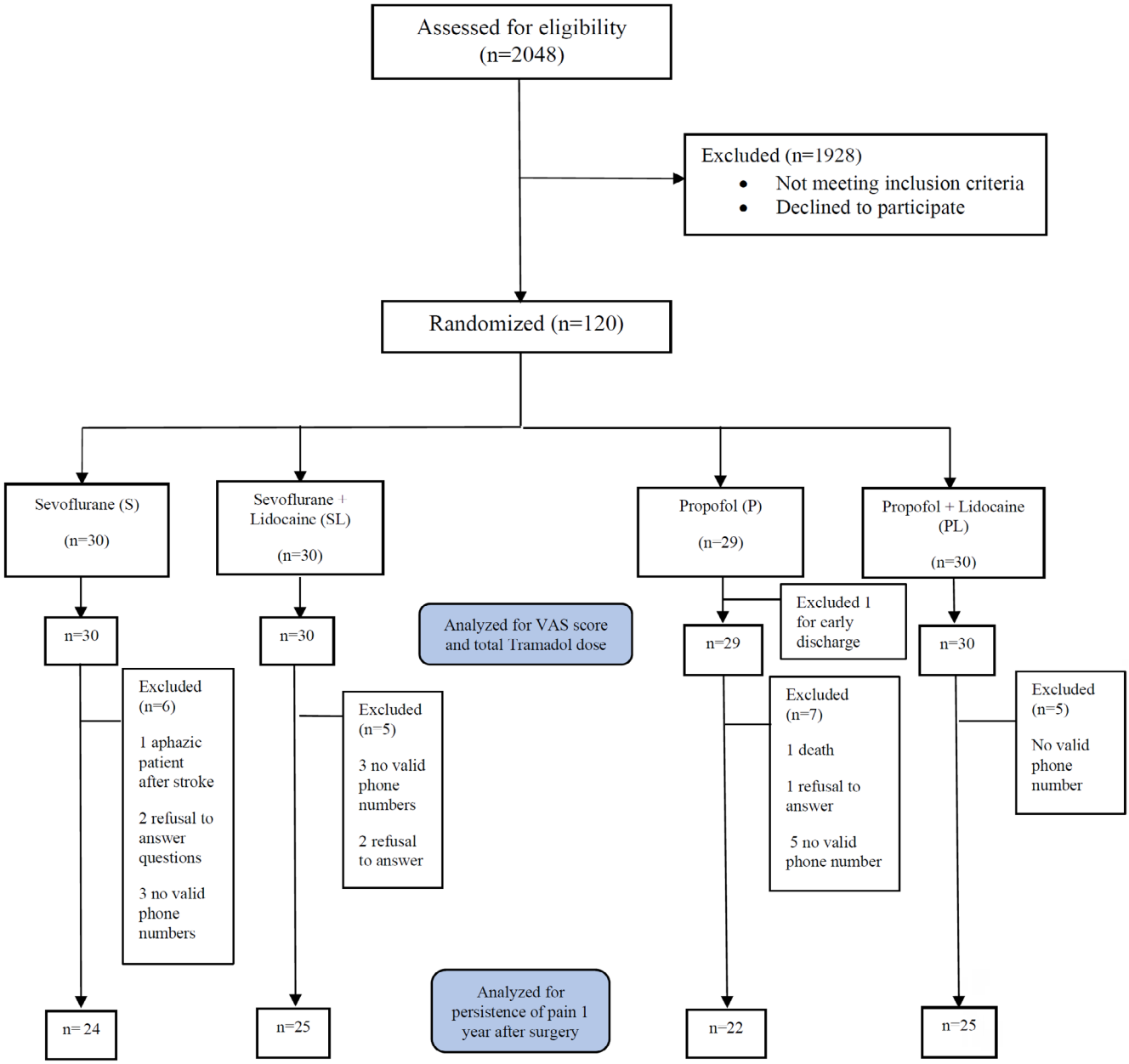

Figure 1. Randomization of patients

Patients enrolled in the study were not known to have metastatic dissemination of the disease before surgery – however, postoperative histopathological data revealed the extension of the disease to the lymph nodes, as shown in the table. Data in the table is presented as the number of patients and percentage of the group in parenthesis (for ASA physical status, preoperative treatment, tumour site, TNM classification), as mean and standard deviation for BMI, and mean and interval limits for the age of the patients. Because not all the patients received preoperative therapy, the values in this section do not ad up to the total of the patients in the group. Regarding TNM classification, because there were cases of bilateral mastectomy with different histopathological grading, the values for the Propofol TIVA-TCI + Lidocaine exceed the total group number.

All patients were monitored in accordance to the standards for Basic Anaesthetic Monitoring of the American Society of Anaesthesiologists.

Anaesthetic induction for all groups consisted in administration of 1-3μg kg^{-1} fentanyl, 1.5-2 mg kg^{-1} propofol and 0.5mg kg^{-1} atracurium. In S and SL groups anaesthesia was maintained with 1-1.5 MAC (minimum alveolar concentration) Sevoflurane in 50-50 mixture of O2 and air as to have a BIS (bispectral index) of 45-55. Intraoperative analgesia was assured by the administration of 100 μg of fentanyl when necessary (defined as systolic arterial pressure or heart rate >20% higher than baseline). Supplementary neuromuscular blockade was provided where indicated by administering 10 mg of atracurium. In groups P and PL, anaesthesia was maintained by administering propofol by TCI Schnider model technique, with a Ce (Effect Site Concentration) of 4μg ml^{-1}, the concentrations being adjusted in 0.2μg ml^{-1} increments, as to maintain a BIS of 45-55. Fentanyl was administered as needed in 100 μg boluses, as well as atracurium 10 mg when there was a need for continuing neuromuscular blockade. A mixture of 50-50 O2 and air was used during intraoperative ventilation. For all groups, at the end of the

Group	Descriptor	Points
Dimension ofpain (1-10)		
1 (temporal)	flickering	1
	quivering	2
	pulsing	3
	throbbing	4
	beating	5
	pounding	6
2 (spatial)	jumping	1
	flashing	2
	shooting	3
3 (punctate pressure)	pricking	1
	boring	2
	drilling	3
	stabbing	4
	lancinating	5
4 (incisive pressure)	sharp	1
	cutting	2
	lacerating	3
5 (constrictive pressure)	pinching	1
	pressing	2
	gnawing	3
	cramping	4
	crushing	5
6 (traction pressure)	tugging	1
	pulling	2
	wrenching	3
7 (thermal)	hot	1
	boring	2
	scalding	3
	searing	4
8 (brightness)	tingling	1
	itching	2
	smarting	3
	stinging	4
9 (dullness)	dull	1
	sore	2
	hurting	3
	aching	4
	heavy	5
10 (sensory miscellaneous)	tender	1
	taut	2
	rasping	3
	splitting	4
11 (tension)	Tiring	1
	exhausting	2
12 (autonomic)	sickening	1
	suffocating	2
13 (fear)	fearful	1
	frightful	2
	terrifying	3
14 (punishment)	punishing	1
	gruelling	2
	cruel	3
	vicious	4
	killing	5
15 (miscellaneous)	wretched	1
	blinding	2
Evaluative dimension of pain		
16 (evaluative)	annoying	1
	troublesome	2
	miserable	3
	intense	4
	unbearable	5
Miscellaneous dimension of pain		
17 (sensory miscellaneous)	spreading	1
	radiating	2
	penetrating	3
	piercing	4
18 (sensory miscellaneous)	tight	1
	numb	2
	drawing	3
	squeezing	4
	tearing	5
19 (sensory)	cool	1
	cold	2
	freezing	3
20 (affectiveevaluative: miscellaneous)	nagging	1
	nauseating	2
	agonizing	3
	dreadful	4
	torturing	5

Figure 2. Part 2 of the McGill questionnaire

surgery neuromuscular blockade was antagonised by administering 2.5 mg neostigmine and 1mg atropine.

For groups SL and PL a bolus of 1.5 mg kg^{-1} 1% lidocaine was administered at the time of anaesthetic induction, followed by a continuous infusion of 1% lidocaine at a rate of 2 mg kg^{-1} h^{-1} throughout the surgery and 1 mg kg^{-1} h^{-1} for the first 24 postoperative hours. For the groups that were not assigned to receive iv lidocaine infusion, an identically packaged saline infusion was prepared by the clinician providing anaesthesia and administered at a rate that mimicked the rate of lidocaine infusion.

Postoperative analgesia consisted in administration of 1 g of paracetamol every 8h (the first dose being administered during surgery) and tramadol 50mg, as rescue analgesia if pain score was >4 using visual analogue scale (VAS).

Postoperative pain scores were recorded every 4h by trained nurses on the surgical ward on the specialized postoperative monitoring chart allocated to each patient entering the study, using VAS scoring system. Tramadol doses were also recorded on the same charts each time the patient needed rescue analgesia. Data on postoperative acute pain was collected from the patient's record after completion of the study. Telephone calls 1 year postoperatively, were made to monitor for chronic pain occurrence, using the part 2 of the McGill questionnaire (Melzack R, 1975). The patients were asked to rate their pain

Table 2. Patient's intraoperative data. Data is presented as mean and standard deviation in parenthesis.

Trial Groups	Sevoflurane (S) (n=30)	Sevoflurane + Lidocaine (SL) (n=30)	Propofol TIVA-TCI (P) (n=30)	Propofol TIVA-TCI + Lidocaine (PL) (n=30)
Type of surgical intervention (n, %)				
Modified radical mastectomy	23 (77)	23 (77)	25 (83)	25 (83)
Quadrantectomy + lymph node removal	7 (23)	7 (23)	5(16)	5 (17)
Duration of anaesthesia (min)				
	74.6 (28.8)	79.1(24.35)	71.5(15)	76.7(22.7)
Intraoperative fentanyl dose (mg)				
Fentanyl (mg)	0.25 (0.05)	0.23 (0.05)	0.24 (0.07)	0.27 (0.08)
Intraoperative crystalloids (L)				
	1 (0.23)	0.98 (0.36)	0.75 (0.32)	0.82 (0.28)
Intraoperative atracurium (mg)				
	36.55 (6.42)	38.83 (7.5)	39.66 (7.42)	41.5 (9.43)
Intraoperative propofol (mg)				
	114.41 (18.99)	123 (29.84)	685.82 (216.61)	739 (231.83)
Total lidocaine dose / 24h (mg)				
		1978.31 (381.34)		1995.12 (434.59)
Intraoperative BIS (mean ±SD)				
	48.1 (2.64)	48.48 (2.83)	48.7 (2.74)	47.17 (2.55)
Intraoperative heart rate				
	68.62 (8.52)	71.03 (9.08)	68.73 (8.31)	67.37 (8.39)
Intraoperative MAP (mmHg)				
	81.11 (5.92)	80.64 (7.66)	81.5 (6.27)	79.66 (6.71)
Nottingham Prognostic Index (mean ±SD)				
	3.2 (0.76)	2.8 (0.64)	2.9 (0.76)	2.8 (0.74)

by choosing the adjectives that best corresponded to their pain from a 20 item list of pain descriptors each of them rated with a certain number of points (Figure 2). The 20 items correspond to 4 categories: items 1-10 to the dimension of pain, items 11-15 to the affective dimension of pain, item 16 to the evaluative dimension and items 17-20 to miscellaneous dimension of pain. Total maximum possible score is 78 points, representing severe pain. The patients, their families, the medical staff involved in the postoperative care, investigators involved in data analysis and interpretation were blinded to the group allocation, while the clinicians providing the anaesthesia and intraoperative management were not.

The primary objective was comparing pain scores between groups to see if continuous lidocaine infusion has a role in the postoperative management of patients undergoing breast cancer surgery. The secondary objective was to compare the need of rescue analgesia between the groups by comparing total tramadol dose administered in the postoperative setting. The third objective was to determine if continuous iv lidocaine administration influences the occurrence of chronic pain 1 year after surgery in the same groups.

The statistical analysis was carried out using the MedCalc Statistical Software version 19.2.1 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020). Quantitative data was expressed as median and 25-75 percentiles (non-normal distribution). Qualitative data was characterized as frequency and percentage. Comparisons between groups were carried out using chi-square or Kruskal-Wallis tests. For repeated measures we used the two-way ANOVA for repeated measures (after the variables were log-transformed). A p value <0.05 was considered statistically significant.

Results

2048 patients were assessed for eligibility between july 2016 and march 2019. 1928 of them did not meet the inclusion criteria for the study. 120 patients were enrolled and randomly assigned to one of four groups (see Figure1). There was no significant differences between the groups regarding patient's demografic data (Table 1), intraoperative data (Table 2) preoperative treatment (chemotherapy or radiotherapy), surgical procedure or the stage of the disease.

Pain assessment using VAS scale every 4 h did not identify any statistically significant difference between the study groups (Table 3A, and Table 3B). The first assessment of pain was done 4h postoperatively in order to exclude the residual effects of intraoperative administration of fentanyl, given that after a fentanyl dose of 100 mcg the analgesic effect persists 30 to 60 minutes (U.S Food& Drug Administration [Internet] 2020). 24h after the surgical intervention the lowest VAS score was in the Propofol TIVA-TCI group : 0 (0;2.75) but there was no significant statistical difference when compared to the other groups (p=0.356).

Table 3 A : Pain scores in the first 24h postoperatively (evaluated at 4h intervals using VAS scoring system); Groups: S- Sevoflurane, SL- Sevoflurane plus iv Lidocaine, P – TIVA-TCI Propofol, PL- TIVA-TCI Propofol plus iv Lidocaine. Data is presented as mean and the 25th and 75th percentile.

Pain score	S	SL	P	PL	P
4 h	3 (1; 5)	4 (0.75;5)	3 (1.25; 3)	3 (0;4)	0.77
8 h	2 (1; 4)	2 (0; 3)	1 (0; 3)	2 (0; 3,25	0.692
12 h	2 (1;4)	1 (0; 3)	1 (0;2)	1 (0;3)	0.124
16 h	1 (0; 3.25)	1 (0; 2)	1 (0; 2)	0 (0;2)	0.293
20 h	1 (0; 4)	1 (0; 2)	1 (0; 3)	0.5 (0; 3.75)	0.723
24 h	2 (0; 3)	0.5 (0;2)	0 (0; 2.75)	1 (0; 2.25)	0.356

Table 3 B : Pain scores in the first 24h postoperatively (evaluated at 4h intervals using VAS scoring system) in groups that had continuous intravenous lidocaine infusion (SL+PL) versus groups that did not (S+P); Groups: S- Sevoflurane, SL- Sevoflurane plus iv Lidocaine, P – TIVA-TCI Propofol, PL- TIVA-TCI Propofol plus iv Lidocaine. Data is presented as mean and the 25th and 75th percentile.

Pain score	S+P	SL+PL	P
4h	3 (1; 4.5)	3 (0.5;5)	0.774
8h	1 (1;3)	2 (0;3)	0.637
12h	1 (1;3)	1 (0;3)	0.129
16h	1 (0;3)	0 (0;2)	0.096
20h	1 (0;3)	0 (0;2)	0.331
24h	1 (0;3)	1 (0;2)	0.514

Table 4. McGill pain score, 1 year postoperatively (groups: S- Sevoflurane, SL- Sevoflurane plus iv Lidocaine, P – TIVA-TCI Propofol, PL- TIVA-TCI Propofol plus iv Lidocaine) Data is presented as mean and the 25th and 75th percentile.

	Group	S	SL	P	PL	P
McGill pain score	Dimension of pain	5 (2;8.75)	5.50 (2.25; 8)	4.50 (2;13.25)	6 (3;13)	0.699
	Affective dimension	0 (0; 0)	0 (0;1.75)	0 (0; 1)	0 (0;1)	0.106
	Evaluative dimension of pain	0 (0;0)	0 (0; 0.75)	0 (0; 1)	0 (0; 1)	0.707
	Miscellaneous dimension of pain	2 (1;3)	2.5 (2; 3.75)	2 (2;4)	3 (2;4)	0.423
Total McGill score		7 (4.25; 12)	8 (5;13)	7 (4; 17.25)	11 (7;20)	0.657

Regarding the need for rescue analgesia using tramadol boluses, when comparing S and P groups versus SL and PL groups, we see a satatistically significant reduction in the mean total dose of tramadol used 100 (50;162.5) mg in S and P groups versus 50 (0; 100) mg in SL and PL groups (p=0.003).

The persistance of pain was evaluated 1 year after the surgical intervention, using part 2 of the McGill questionnaire. There was no diference in overall pain scores in the study groups (Table 4) nor between the different dimensions of pain evaluated with this method. No cases of lymphoedema that could influence the evaluation of chronic pain were registered at the moment the thelephone call was made, although the 1 year asessment may have been too early for lymphoedema to develop.

Discussion

The first objective of this study is to compare the postoperative pain scores between the study groups in order to assess the role of continuous iv lidocaine infusion in the postoperative setting in breast cancer surgery. Postoperative pain has inflammation and nuropathic components (Kehlet et al 2006) and postoperative analgesia needs to target those components in order to be effective. Lidocaine is known to have analgesic, anti-hyperalgesic, anti-inflammatory, properties, rendering it a possible useful tool in the management of postoperative pain (Kranke et al 2015). The distribution of lidocaine in well perfused tissues, skeletal muscle and fat (De Menenzes et al 2014) makes it a convenient analgesic for breast cancer surgery. The benefits of IV lidocaine have been explored, due to the known properties and safe profile of this drug, with good results in abdominal surgery manifested as early recovery, lower pain scores, lower opiod consumption, shortening the length of in hospital stay, faster recovery of bowel function and greater patient satisfaction (Eipe et al 2016). Though the effect of iv lidocaine seems to be well established for abdominal surgery (Weibel et al 2016), for breast cancer surgery there are conflicting results regarding its efficacy (Chang et al 2017, Terkawi et al 2014, Grigoras et al 2012). We tested the hypothesis that lidocaine infusion would provide better analgesia in the postoperative period. Our results regarding the effect of lidocaine on postoperative acute pain revealed no significant difference in the postoperative VAS scores between the study groups – continous iv lidocaine infusion showing no benefit. We expected that a prolonged lidocaine infusion would decrease pain scores more, compared to other studies where the duration of infusion was stopped immediately after end of surgery (Kim et al 2017) or 1h (Byrne et al 2016) and 2h (Kim et al 2017) in the postsurgical setting. Our results may be attributable to the dosing regimen: 1% lidocaine iv infusion of 2 mg kg-1 h-1 during surgery and 1 mg kg-1 h-1 for the first 24 postoperative hours– in accordance to the most frequent used intervals: 1-2 mg kg-1 h-1 (Terkawi et al 2014), also chosen because of the narrow therapeutic index of the drug and the impossibility of determining lidocaine plasma concentration in the hospital setting. Also we wanted to see if usage of a dosing regimen in the lower range of the interval, that is less likely to produce adverse effects, would be beneficial in controlling postsurgical pain. As shown in Table 3A and Table 3B, there were no differences in the study groups between registered VAS scores.

The secondary objective was to compare the need for rescue analgesia between study groups that received iv lidocaine and those who did not. Our results show a statisticaly significant decrease in the total dose of tramadol received after the surgical intervention (p=0.003) for the groups that had a continuous lidocaine infusion. The results are in contrast to the results

obtained until now that show no benefit in lidocaine administration on total analgesic consumption (Dunn et al 2017). Though the pro-tumoral effect of tramadol has not been yet researched we have to bear in mind the effects of opioids on angiogenesis and their potential for favouring tumoral progression (Byrne et al 2016) and inducing immune supression. This aspect can prove beneficial in breast cancer surgery, lowering the need for opioid consumption in the postoperative setting and avoiding their adverse effects related to pro-tumoral behaviour. Also, other benefits of iv lidocaine infusion in the perioperative setting besides lowering the opioid requirement include: a decrease of cancer cell migration via Src inhibition, the reduction of cell excitability by blocking VGSC (voltage gated sodium channels), a reduction of DNA methilation, which all contribue to decreasing the potential of metastatis (Levins & Buggy 2015). Chronic pain is defined as "pain that extends beyond the expected period of healing", sometimes exceeding 6 months (Kandil et al 2017). The importance of efficient pain control after surgical intervention cannot be stressed enough. Chronic pain can interfere with occupational performances and daily domestic activities or have psychological consequences, influencing the social and economical reinsertion in society of patients that have undergone breast cancer surgery (Macrae 2001). Prevention of chronic pain is important for the physical and emotional health of this patient category. Regarding the third objective of the study – prevention the occurrence of chronic pain, lidocaine administration in the perioperative setting did not seem to influence pain scores (Table 4). Our results contrast those from other studies (Dunn et al 2017) that show a benefit of iv lidocaine in preventing chronic pain after breast surgery. Though the duration of lidocaine infusion was longer in our study compared to others (Kim et al 2017; Byrne et al 2016), there was no benefit on the long term. Better results may be seen if a higher dose (2-3 mg kg^{-1} h^{-1}) would be administered over the same time period (up to 24h postoperatively), but supervision in an high dependency unit may be needed and lidocaine concentration may be necessary to be determined, in order not to reach toxic levels and prevent adverse events. Also, the 1 year period set for chronic pain evaluation may have contributed to attenuation and homogenization of the results.

Conclusion

The benefit of a low dose lidocaine infusion may come from the significant lowering the need for rescue analgesia observed in our study, that can diminish opioid administration and their consecutive effects (PONV, dizziness, prolonged recovery, possible promotion of angiogenesis) in the postoperative setting. Continuous infusion of iv lidocaine did not show any benefit in reduction of pain scores in the postoperative setting nor did it lower the incidence of chronic pain 1 year after the surgical intervention. Also, continuous infusion of lidocaine at higher doses for at least 24 h after surgery needs to be investigated in order to determine its place in the postoperative management of breast cancer patients.

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Authors

•Elena V Galoș, 1st Department of Anaesthesiology and Intensive Care, Iuliu Hațieganu University of Medicine and Pharmacy, 8 Victor Babeș street, Cluj-Napoca, Cluj, Romania; e-mail: draghiciuelena@yahoo.com

•Tiberiu-Florin Tat, Prof. Dr. Ion Chiricuță Institute of Oncology, 34-36 Republicii street Cluj-Napoca, Cluj, Romania. e-mail: dr_tibi@yahoo.com

•Popa Răzvan, Prof. Dr. Ion Chiricuță Institute of Oncology, 34-36 Republicii street Cluj-Napoca, Cluj, Romania. e-mail: p.razvan@gmail.com

•Ștefan Vesa, Department of Pharmacology, Toxicology and Clinical Pharmacology, Iuliu Hațieganu University of Medicine and Pharmacy, 8 Victor Babeș street, Cluj-Napoca, Cluj, Romania; e-mail: stefanvesa@gmail.com

•Daniela C Ionescu, 1st Department of Anaesthesiology and Intensive Care, Iuliu Hațieganu University of Medicine and Pharmacy, 8 Victor Babeș street, Cluj-Napoca, Cluj, Romania; e-mail: dionescuati@yahoo.com

•Carmen-Mihaela Mihu, Department of Histology, Iuliu Hatieganu University of Medicine and Pharmacy, 8 Victor Babeș street, Cluj-Napoca, Cluj, Romania; e-mail: carmenmihu2004@yahoo.com

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