VOLUME - 10, ISSUE - 04, APRIL- 2021 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Breast Surgery

SHORT TERM OUTCOMES OF A COMPARATIVE ANALYSIS BETWEEN LOCAL ANESTHETIC WOUND INFILTRATION AND REGIONAL ANESTHESIA IN BREAST SURGERY: SHOULD WE OPT FOR A SELECTIVE APPROACH?

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ABSTRACT

Background: Full short-term effects of regional anesthesia in breast surgery is not well known. We aimed to assess any differences in the short-term outcomes of regional block and local anesthetic (LA) wound infiltration in breast surgery.

Materials and methods: A prospective non-randomized observational study of elective breast surgical procedures between 01/06/2018 and 28/02/3019 was performed at a district general hospital in the North-West England. Data comprised of patient- and procedure-specific demographics, relevant health conditions, pain scale, blood pressure, analgesia requirement, Post-operative Nausea and Vomiting (PONV) score and Length of stay (LoS). Operations were classed as minor/ moderate and major. Regional anesthesia (RA) comprised of paravertebral, intercostal, pectoral and serratus blocks.

Results: A total of 143 events (regional anesthesia, n=58; LA wound infiltration, n=85) were analysed. Reduced pain score and longer anesthetic time were noted in the regional anesthesia group ($p<0.001$). A trend of reduced strong opioid requirement was also noted in the major procedure group receiving regional anesthesia. PONV scale was higher in the major surgery groups, significantly so in the LA group ($p<0.001$). No significant association was noted with various past medical histories, and LoS. A significant increase in occurrence of wound-site haematoma (5.6%) along with per-operative hypotension was noted in the paravertebral block group. Levo-Bupivacaine was associated with least overall opioid requirement ($p=0.01$).

Conclusions: A selective approach to provide regional anesthesia using Levo-Bupivacaine in major breast cases, irrespective of common health conditions, would likely to result in reduced pain score and opioid requirements, and offset the longer anesthetic time. Association between haematoma formation and paravertebral block merits further larger study.

Plain Language Summary

- Regional anesthesia in breast surgery warrants specialist skill, extra time and has potential side effects as well as benefits.
- Short term benefits of regional anesthesia in breast surgery were assessed in this non-randomized study in comparison to traditional local anesthetic wound infiltration.
- Most benefits, in terms of improved pain score and reduced morphine requirements, were noted in association with regional anesthesia using Levo-Bupivacaine in major breast cases. This would allow a selective approach whilst planning for most effective anesthetic and analgesic effect in breast surgery.
- Higher occurrence of post-operative wound haematoma was noted mostly in association with paravertebral block, the particular type of regional anesthesia where drop of blood pressure was also significant. Further study would help clarify the significance of these findings.

KEYWORDS : "Operative procedures", "Breast", "Regional anesthesia", "Local anesthetics", "PONV", "Analgesia"

Introduction:

"He that sleeps feels not the toothache" -William Shakespeare (1564 - 1616)[1]

"The state should, I think, be called 'anesthesia' this signifies insensibility" -William Morton (1819 –1868)[2]

"The only weapon with which the unconscious patient can immediately retaliate upon the incompetent surgeon is hemorrhage" -William Stewart Halsted (1852 - 1922)[3]

It sounds like a story of three Williams. Shakespeare's observation (Cymbeline: Act 5, Scene 4) explains why attempts to alleviate the pain of disease, injury or simple surgical procedures by producing unconsciousness are almost as old as civilization, although the techniques were crude.[1] William Morton, credited as the pioneer of general anesthesia, successfully demonstrated effect of ether anesthesia in 1946.[2] The enormous potential of wider use in surgery was recognized at once.[3] Subsequent developments culminated in widespread use of anesthesia that saw a meteoric rise in surgical procedures at the end of 19th Century. Amongst the first to seize the opportunity was William Halsted, who introduced radical approach to the breast cancer surgery in 19th century and is widely considered as founder of modern surgery.[3,4] The focus was strictly on radical surgery, which relied profoundly on development in the fields of anesthesia and asepsis.[5]

Fast forward to 21st century, the approach to breast cancer has seen fundamental changes. In recent years, controversy has centered on whether breast cancer is a systemic or local disease at inception.[6] Surgery remains the first-line treatment for early, localized, or operable breast cancer, is performed in

conjunction with various neo-adjuvant or adjuvant treatments.[7-9] One concerning problem that affects breast cancer patients after surgery is the pain, which has been associated with increased incidence of nausea and vomiting, cardiovascular instability, disturbance of sleep, delays in postoperative patient mobilization and length of stay.[10] Regional anesthesia can help in reducing post-operative pain. Furthermore, stress response, caused by surgery, also inhibits the immune system, and can be associated with the release of tumour cells systemically.[11] Retrospective studies have hinted that regional anesthesia can play a protective role in cancer surgery. Therefore, a suitable anesthetic technique such as regional anesthesia can play a vital role in mitigating both short term ill effects of post-operative pain, and perhaps provide a long-term benefit in reduction of local recurrence.[10,11]

The site of the current study is a 760-bedded district general hospital with teaching and research affiliations to neighboring universities, catering approximately 440,000 population in the North West of England.[12,13] The breast unit deals with approximately 300 new cancers every year. All breast surgery take place on site, led by a team of three consultant breast and oncoplastic surgeons. The procedures that entail regional anesthesia involve a few dedicated consultant anesthetists with special interest and experience in regional anesthesia in breast surgery. Limited human resource allocation, time constraints, potential complications have all raised question about the need for providing regional anesthesia in all cases of breast surgery.

When it comes to anesthetic analgesia in elective breast surgery, often the choice remains between regional anesthesia and rather traditional local anesthetic (LA) wound infiltration. Whilst some studies have attempted to explore the effect of regional anesthesia on survival of breast cancer, others have looked mostly at suitability of a specific type of regional anesthesia in a specific breast surgical procedure by focusing mostly on pain control and post-operative nausea and vomiting (PONV).[11,14-16] None of the studies actually explored the short-term outcomes of regional anesthesia as well as LA wound infiltration in breast surgery as a whole, in the context of potential biases and physiological changes. Current literature does not provide a clear answer whether 'all' patients undergoing breast surgery would be befitted by regional anesthesia, or should a 'selective' approach be more productive?

Aims:

The primary aim of the study was to assess and compare short term outcomes (such as changes in blood pressure, nausea & vomiting, pain control, requirement of analgesia, length of stay and complications) between local anesthetic wound infiltration and regional anesthesia in breast surgery, in the context of various past medical histories, type of surgery and confounding factors. The secondary aim was to identify any practices or subgroups, where regional anaesthesia would be better suited than local anaesthesia.

Materials and methods:

Patients were listed and consented for relevant procedures, once the decision was made in the breast clinic, with involvement of multidisciplinary team and breast care specialist nurses, as appropriate. Patients were routinely assessed in the pre-operative clinic and their conditions were optimized, if and when necessary, and given a planned date for surgery. On the day of operation, patients were reviewed by the anesthetists and surgeons, and options of anesthetic analgesia were discussed in full.

***Setting*:** District General Hospital in the North-west of England, UK

***Study period*:** Between 1st June 2018 and 28th February 2019

***Inclusion criteria*:** All successive patients undergoing elective breast surgery above the age of 18.

***Exclusion criteria*:** i) Patients below the age of 18; ii) Refusal to have regional anesthesia or LA wound infiltration; iii) those who concomitantly received both regional anesthesia and local anesthetic infiltrations and iv) emergency procedures such as drainage of abscess or evacuation of haematoma.

***Type of study*:** Prospective observational study involving data collection of two groups, namely regional anesthesia and local anesthetic wound infiltration.

***Consent*:** There was no requirement for ethical approval or informed consent.

***Randomization*:** There was no randomization. The decision of regional anesthesia or LA wound infiltration was taken on the day as per the routine practice of the relevant anesthetist following discussion with the patient, without any prior randomization. However, the allocation of anesthetists to breast surgery lists was random, and purely dependent on the anesthetic rota.

***Type of the procedure*:** surgical procedures were divided into two groups-

i) Minor or moderate, such as excision biopsy of breast or axillary lump, wide local excision (with or without wire guidance) of carcinoma breast, mammary duct excision and lymph node biopsy; and
ii) Major, such as simple mastectomy, axillary node clearance, therapeutic mammoplasty, augmentation and reduction (with or without mastopexy), and reconstruction (immediate or delayed).

***Regional anesthesia (RA)*:** Regional anesthesia involved thoracic paravertebral (PVB), intercostal, pectoral and serratus blocks (either in isolation or combination). PVB was usually reserved for major cases entailing long duration. Selection of the rest of the RA technique dependent on the type (minor/ moderate vs. major) of surgery and location of incision/ site of dissection. The regional anesthesia was performed by the anesthetist under real time ultrasound guidance in the anesthetic room, usually after induction of anesthesia. Multiple injections were usually given without insertion of any indwelling catheter for infusion. Asepsis was maintained during infiltration and 18G-22G needles were used for block.

i) PVB was performed, as described by O'Riain *et al* (2010).[17] Paravertebral block typically involved targeting the paravertebral space (PVS), which has been classically described as a triangular-shaped area bounded medially by the vertebral bodies, intervertebral discs and intervertebral foramina; anteriorly by the parietal pleura and posteriorly by the superior costotransverse ligaments, ribs and transverse processes.[18]
ii) Intercostal block involved infiltration around intercostal neurovascular bundle at the upper part of intercostal space, as described by Bonica *et al* (1990).[19]
iii) Pectoral blocks (Pecs-I and Pecs-II) are superficial inter-fascial plane blocks, which grant access to the branches of the brachial plexus that supply the pectoral muscles and upper anterior thoracic wall, and were performed as described by Blanco *et al* (2011). Pec-1 involved injecting LA in the fascial plane between pectoralis major and minor muscles (performed with the patient supine, either with the arm next to the chest or abducted at 90 degrees), adjacent to the pectoral branch of the thoracoacromial artery. A Pecs-2 block consisted of a Pec-1 injection, plus a

second injection made under pectoralis minor muscle in the anterior axillary line at the level of the fourth rib.[18,20]

iv) Serratus anterior block involved in-line needling and placement of local anesthetic solution either superficial or deep to the serratus anterior muscle in the midaxillary line at the level of the fifth rib, also as described by Blanco *et al* (2013).[21]

***Local anesthetic (LA) wound infiltration*:** The infiltration was performed by the surgeon during operation using a 18G or 20G needle.

***Local anesthetic agent*:**

i) Types- Bupivacaine and Levo-Bupivacaine; patients with higher risk profile usually received Levo-Bupivacaine.
ii) Dosage- 3 mg/kg of Bupivacaine or Levo-Bupivacaine, up to a maximum of 150 mg.
iii) Strengths- 0.5%, 0.25% and 0.375% (Bupivacaine); and 0.25% and 0.375% (Levo-Bupivacaine). Appropriate strength was selected to match the required volume that would deliver maximum allowed dosage without compromising safety.
iv) Anesthetic induction time-The actual period of time that the patient stayed in the anesthetic room, which included time for induction and regional block, where applicable.

Blood pressure (BP): Both systolic and mean BP were recorded (on admission and during the procedure) in mm of Hg.

***Pain score*:** A 11-point verbal numerical rating scale was used to assess intensity of pain (no pain= 0; mild, moderate, severe, and very severe pain= 1-10).[22] The maximum single most pain score during post-operative period was recorded.

***PONV*:** PONV intensity scale was used (significant PONV; none/ no significant PONV).[23] The maximum PONV scale during post-operative period was recorded.

***Analgesia*:** Analgesia administered in the ward during post-operative period was recorded as simple analgesia (such as Paracetamol and/or Ibuprofen), weak opioid (such as Codeine, Dihydrocodeine and Tramadol), and strong opioid (morphine). Pain score guided the type of post-operative analgesia required in the ward, namely simple analgesia for mild pain, mild opioid for moderate pain and morphine for severe or very severe pain. The dispensation of analgesia dependent on the discretion of the nursing staff in the ward, with guidance from the anesthetist, if necessary. In case of more than one type of analgesia being dispensed to the patient over a course of time, the most potent analgesia was recorded for the purpose of the study.

***Complications*:** Both LA (such as allergy, neurovascular damage, pneumothorax, local bruise) and surgical (haematoma) complications were recorded.

***Discharge and Follow-up*:** Patients were reviewed post-operatively and discharged as per pre-operative plan, subject to acceptable control of PONV, pain, stable states of observations and wounds, and satisfactory social circumstances. All patients were routinely followed-up in the surgical clinic in 2-4 weeks' time.

***Histology*:** Type of histology was grouped as i) benign (diagnostic excision showing a benign condition) or not applicable (aesthetic procedure) and ii) malignancy.

***Source of data collection*:** Case notes, digital archives and Operating Room Management Information System (ORMIS©).

Data collected:

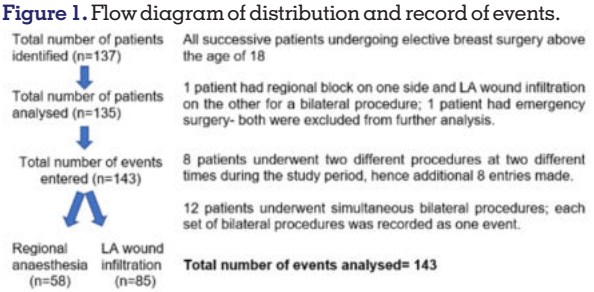
i) 20-point past medical conditions and various relevant factors
ii) (Age, concerned Anesthetists and Surgeons; Diabetes, Hypertension, Cardiac condition, Chronic pain, Connective tissue disorder, Immune-modulator, Antiplatelet/ anticoagulant, Neo-adjuvant chemotherapy, Prior breast surgery, Prior radiotherapy, Active smoking, BMI; Type, Strength & Volume of LA, Pre-operative BP).
iii) 18-point procedural and outcome measures
iv) (Anesthetic induction time, Breast procedure, Reconstruction, Axillary procedure, Verbal numerical rating pain scale, PONV score, Simple analgesia, Weak opioid, Strong opioid, Average & Lowest systolic per-operative BP, Average & Lowest mean per-operative BP, Length of stay, Haematoma formation, Complications of regional block & LA wound infiltration and Histology).

***Statistical analysis*:** Chi-square, Fisher's Exact test, Student's t-test, One-way Anova and Kaplan-Meier tests were performed using SPSS V26 (IBM® corporation, New York, USA). A p-value of <0.05 was considered to be statistically significant.

Results:

A total of 137 patients were identified and 143 events were analysed. Fifty-eight patients received regional anesthesia and eighty-five patients received LA wound infiltration. Figure 1 depicts distribution of all patients.

Figure 1. Flow diagram of distribution and record of events.



There was no significant difference amongst most of the demographics (patient and procedure), past medical histories and various confounding factors [Table 1]. The areas where statistical significances were noted were age; type, strength, and volume of LA; anesthetic time for induction and histology. A separate sub-group analysis showed that those with malignant conditions were older (62.0± SD 13.0), compared to those who had benign (50.6± SD 17.7) conditions ($p<0.001$).

Table 1. Distribution of patient and procedure demographics, past medical histories and various confounding factors as per the type of intervention (n=143). All ordinal and ratio data have been expressed as ± SD, where applicable.

		LA wound infiltration	Regional anaesthesia	p-value
Median age at diagnosis (years)		59 (range 21-94)	61 (range 41-89)	**0.002**
Diabetes	No	82	55	0.63
	Yes	03	03	
Hypertension	No	66	48	0.45
	Yes	19	10	
Cardiac condition	No	78	52	0.66
	Yes	07	06	
Chronic pain	No	80	56	0.50
	Yes	05	02	
Connective tissue disorder	No	82	56	0.69
	Yes	03	02	
Immune-modulator drug	No	83	54	0.18
	Yes	02	04	
Antiplatelet/ anticoagulant	No	80	50	0.10
	Yes	05	08	

Neo-adjuvant chemotherapy	No	71	49	0.87
	Yes	14	09	
Prior breast surgery	No	57	37	0.68
	Yes	28	21	
Prior radiotherapy	No	77	50	0.41
	Yes	08	08	
Active smoking	No	77	53	0.87
	Yes	08	05	
Mean BMI		27.7(±5.4)	27.3 (±6.2)	0.69
Type of LA	Bupivacaine	75	28	**<0.001**
	Levo-Bupivacaine	10	30	
Strength of LA	0.25%	67	44	**<0.001**
	0.5%	18	06	
	0.375%	00	08	
Mean volume of LA (ml)		37.1(±12.9)	42.5 (±10.3)	**0.01**
Mean anaesthetic time (min)		5.8(±12.5)	26.7 (±8.7)	**<0.001**
Breast procedure	Minor/ moderate	38	22	0.42
	Major	47	36	
Reconstruction	No	67	39	0.12
	Yes	18	19	
Axillary procedure	No	39	23	0.46
	Yes	46	35	
Histology	Benign	62	6	**0.02**
	Malignant	23	52	

(SD= standard deviation; LA= Local anaesthetic; BMI= Body Mass Index)

Table 2 shows associations between type of the procedure and pain score as well as PONV scale. Statistically significant higher occurrence of pain score was noted following major surgery, in both LA and RA groups. However, relatively lower incidences of severe and very severe pain were noted in the group of patients who underwent major surgery and received regional anaesthesia, compared to those who received LA. Similarly, PONV scale was higher in the major surgery groups, significantly so in the LA group (p<0.001). Also, the relative incidence of significant PONV in the major surgery group was lower (2.7%) amongst patient who received regional (2.7%), than local anaesthesia (12.7%).

Table 2. Association between the mode of intervention and type of the procedure, verbal numerical pain rating scale (NPRS) and post-operative nausea and vomiting (PONV) scale.

		LA infiltration			Regional block		
		Minor/ moderate	Major	p-value	Minor moderate	Major	p-value
Verbal NPRS	None	13	01	0.0003	06	07	0.009
	Mild	22	29		12	10	
	Moderate	03	14		02	19	
	Severe	00	02		01	00	
	Very severe	00	01		01	00	
PONV Scale	Not raised/ Insignificant	37	41	<0.001	22	35	0.44
	High/ Significant	1	6		00	01	

Requirement of strong opioid was generally low in either group requiring local or regional anaesthesia. A trend of lesser requirement of strong analgesia (morphine) was noted particularly amongst the 'major surgery' group receiving regional anesthesia, compared to LA wound infiltration, but it was not statistically significant (p=0.33) [Table 3].

Table 3. Procedure specific morphine requirement as per the type of intervention (LA= Local anaesthesia' RA= Regional anaesthesia).

	Minor/ Moderate procedure			Major procedure		
	Morphine	Other analgesia (None/ simple analgesia/ mild opioid)	p-value	Morphine	Other analgesia (None/ simple analgesia/ mild opioid)	p-value
LA	0 (0%)	42 (64.6%)	0.18	7 (70%)	36 (53.7%)	0.33
RA	1 (100%)	23 (35.4%)		3 (30%)	31 (46.3%)	
Total	*1*	*65*		*10*	*67*	

Mean length of stay (LoS) was 0.47 ± SD 0.77 (range 0 - 5) days. As far as LoS, and day case surgery were concerned, there was no significant association with either of the intervention group. [Table 4]. A sub-group analysis showed a higher occurrence of major cases in the regional anesthesia group (n=36 out of 58; 62%), compared to LA infiltration (n=47 out of 85; 55.2%) group, although it was not statistically significant [p=0.42].

Table 4 Blood pressure recordings and length of stay as per the type of intervention.

		LA wound infiltration (mean ± SD)	**Regional anesthesia** (mean ± SD)	p-value
Lowest systolic per-operative BP		92.4 ± 16.1	90.1 ± 17.2	0.41
Lowest mean per-operative BP		66.5 ± 07.9	66.4 ± 10.7	0.94
Drop of systolic BP during surgery (compared to pre-operative systolic)		49.7 ± 25.4	55.3 ± 19.1	0.15
Drop of mean BP during surgery (compared to pre-operative mean)		33.0 ± 16.0	37.1 ± 13.4	0.11
Drop of systolic BP during surgery (average – lowest systolic BP)		13.8 ± 11.7	38.6 ± 12.5	**0<0001**
Drop of mean BP during surgery (average – lowest mean BP)		07.5 ± 06.9	08.2 ± 09.5	0.61
Length of stay (LoS)	Day (0-5)	0.38 ± 0.69	0.60 ± 0.87	0.10
	Day surgery	61	33	0.06
	Inpatient	24	25	

[SD= standard deviation; LA= Local anesthetic; BP= Blood pressure (mm of Hg)]

Table 5 shows the association between type of LA agent and simple analgesia/ opioid requirement. Levo-Bupivacaine was significantly associated with reduced post-operative overall opioid (both weak and strong) intake, in comparison to Bupivacaine. Strength (percentage) of LA had no significant impact on analgesia requirement.

Table 5. Association between type and concentration of Local Anaesthetic and analgesia requirement.

		None or simple analgesia	Weak or strong opioid	p-value
Type	Bupivacaine	75	29	0.018
	Levo-Bupivacaine	20	19	
Strength	0.375%	6	3	0.076
	0.25%	70	42	
	0.5%	20	3	

Out of a total of 21 anesthetists involved in the study, 12 provided regional blocks. Most (49 out of 59; 83%) of the regional blocks were performed by 4 anesthetists (p<0.001).

Higher volume of LA was associated with higher change of per-operative systolic BP (compared to pre-operative recordings) [p=0.29].

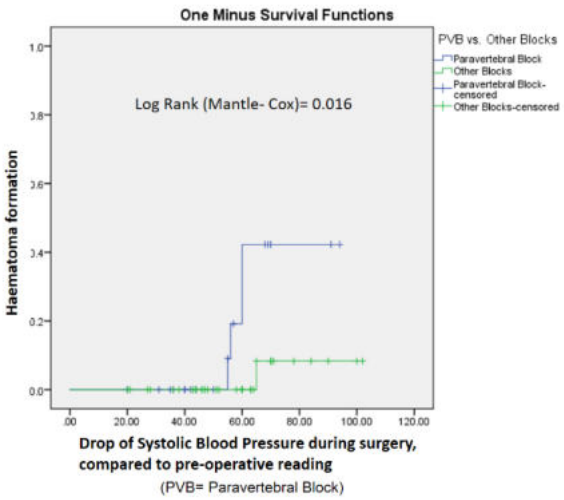
There was no documented complication related to regional block or LA wound infiltration. There was no record of failed block. A total of 8 wound hematomas took place, which required evacuation in 5 cases. Occurrence of haematoma was almost double in the regional anesthetic group (8.6%), compared to LA wound infiltration group (3.6%). However, the association was not statistically significant (p=0.20). A subgroup analysis showed that a significantly higher proportion of haematoma was encountered in the paravertebral block group (4 out of 21; 19%), compared to the rest (1 out of 37; 2.7%) of the regional anesthesia techniques (p=0.03) [Table 6]. There was no significant association between occurrence of haematoma and operating surgeon (p=0.42).

Table 6. Occurrence of haematoma formation according to intervention.

		Haematoma formation		p-value	
		No	*Yes*		
Regional anesthesia	**Paravertebral**	17	04	<0.01	0.20
	Paravertebral & Pectoral	02	00		
	Paravertebral & Serratus	03	00		
	Pectoral	10	01		
	Pectoral & Serratus	18	00		
	Serratus	01	00		
	Intercostal	02	00		
LA wound infiltration		82	03		

Table 4 also showed various BP recordings during surgery, showing a significant higher drop in systolic BP (compared to average per-operative systolic) in the regional anesthesia group (p<0.001). A separate regional anesthesia sub-group analysis showed a significant drop of systolic BP during operation (compared to preoperative systolic) amongst those who later developed haematoma (59.2 ± SD 3.9), compared to those who did not (55.0 ± SD 19.9), [p=0.015]. Kaplan Meier graph also confirmed above findings [Figure 2].

Figure 2. Kaplan-Meier graph showing change of blood pressure as per haematoma formation according to intervention.



Discussion:

Incidence rates for breast cancer are projected to rise by 2% in the UK between 2014 and 2035, to 210 cases per 100,000 females by 2035.[24] Surgical resection was one of the first effective treatments for breast cancer and continues to play a critical role in this regard.[7,8] We carried out a detailed search of English literature using PubMed, Ovid MEDLINE®, Google Scholar, EMBASE, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature databases, using the key words 'breast surgery', 'regional anesthesia', 'analgesia', 'complication', 'hypotension', 'PONV', 'haematoma' and 'length of stay'. Post-surgical pain following breast surgery came to light to be a common occurrence, with most studies reporting the incidence of moderate-to-severe postoperative pain reaching 25–30%.7,10 International Association for the Study of Pain (IASP) society defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.[25] PONV is also a common distressing symptom or side effect after surgery and anesthesia. It can cause complications such as wound dehiscence, electrolyte imbalance, increased pain, dehydration and aspiration.[26] Use of regional anesthesia has been associated with a lower incidence of PONV.[27] Interestingly, the use of regional anesthesia techniques may modulate the immune system, likely via interleukins (IL). Increased IL-10 levels after propofol/paravertebral anesthesia for breast cancer has been reported, compared to sevoflurane/opioids.[7] Preclinical and clinical studies suggest that the anesthetics and adjuvants given in the perioperative period can affect cancer recurrence and survival, perhaps tipping the balance in some instances to determine whether cancer progresses or regresses.[11]

Multimodal analgesia for breast surgery should include local or regional analgesic techniques. Regional anesthetic or analgesic blocks can be performed by either an anterior or posterior approach to achieve optimum analgesia. Anterior-approach blocks include pectoral nerve, serratus anterior plane, interpleural, and intercostal nerve blocks. Posterior-approach blocks include thoracic epidural and paravertebral blocks and newer approaches such as erector spinal plane blocks. The use of ultrasound in regional anesthesia has improved the safety of the various techniques and also broadened their scope.[28] With recent development of onco-plastic procedures, more and more complex surgeries, including breast reconstructive surgeries, are now carried out routinely. These procedures are frequently associated with post- operative pain and prolonged hospital stays and related costs, and regional anesthesia may be helpful in these situations. Complications of regional anesthesia include LA intoxication, vasovagal reaction, vascular puncture, neural damage pneumothorax, intrathecal or epidural spread and sympathetic block leading to hypotension and hemodynamic instability,[29,30] The latter are complex, interactive, and as yet, the underlying mechanisms are not fully understood.[31] However the complications don't always get fully reported.[32]

Needless to say, regional anesthesia has an important role to play in breast surgery and needs further evaluation. However, a short-term study would not be able to address a long-term effect such as disease recurrence or survival. Therefore, we focused in our study on short-term relevant aspects of the analgesic effect of regional anesthesia and LA wound infiltration in our study. Given the complex, sometimes inconclusive, if not contradictory findings, it is not unreasonable to consider the possibility of potential biases that would explain the differences in findings. Therefore, we aimed to assess the outcomes of both LA wound infiltration and regional blocks in breast surgery as a whole, in the context of 20-point past medical histories and relevant factors. We also measured 18-point outcome variables. This comprehensive evaluation was undertaken in order to address potential biases and confounding factors. A combination (n=7) of four different types of regional blocks (namely paravertebral, pectoral, intercostal and serratus

blocks), were included in the study. Selection of the type of block depended on nature and location of the procedure and anesthetist's choice. We considered each simultaneous bilateral procedure as one case as it is not possible to distinguish effect of analgesia on each side separately in relation to PONV, pain score, and analgesia requirements. For the same reason, we also excluded anyone who had LA wound infiltration on one side and regional block on the other, to save any confusion.

As far as the past medical histories/ conditions and various confounding factors are concerned, no significant difference was noted in majority of the cases [Table 1]. This is therefore reassuring that the choice of anesthetic analgesia can be made without the influence of common health conditions. Not surprisingly, anesthetic induction time was significantly higher in the regional anesthesia group, reflecting the extra time needed to undertake this additional step. A significant difference in use of LA was noted, perhaps echoing a heterogenous group of procedures performed, which warranted different volumes and strengths to provide a safe and efficacious dosage. This would explain the significant variations noted in the types, concentrations and volumes of LA in two groups of intervention [Table 1]. A higher incidence of malignant histology was noted in the regional block group, reflecting perhaps choice of regional anaesthesia to provide a potential long-term survival benefit in cancer cases. This would also explain the higher age in the regional anesthesia group as those with malignant conditions were significantly older compared to those who had benign conditions.

A significantly lower pain score and a trend of reduced morphine requirement were noted amongst the patients who underwent major procedures in the regional anesthesia group, compared to LA wound infiltration group [Tables 2 and 3]. Reduced pain score, noted in our study is in accordance with the findings noted by other studies.[7,16] However, lack of statistical significance in reduced analgesia requirement amongst major procedures noted in our study could be a reflection of including unselected consecutive 'all' breast surgery and multiple types of block for providing regional anesthesia in the study, rather than a definitive procedure (such as mastectomy) and specific block (such as paravertebral block).

Literature review has shown that regional anesthesia improves PONV.[27] The current study showed no significant difference in terms of PONV in RA groups. This is because of the simple fact that the occurrence of significant PONV as such was extremely low in both groups (n=4 out of 142; 2.8%) [Table 2].

Association between type of LA and analgesia requirement showed an interesting finding. Levo-Bupivacaine was associated with reduced opioid requirement [Table 5]. The choice of local anesthetic is influenced by efficacy and safety. Bupivacaine has so far been our default LA of choice. In fact, Bupivacaine, is one of the most widely used long acting local anesthetic agent in both surgery and obstetrics, However, there has been reports of fatal cardiotoxicity, usually after accidental intravascular injection.[33] Levobupivacaine, the single enantiomer version of bupivacaine, offers a new long acting local anesthetic, clinically equivalent in anesthetic potency to bupivacaine, but with a significantly reduced risk profile in terms of central nervous system and cardiac risks than Bupivacaine.[33] Given the safer profile and reduced post-operative opioid analgesic, as noted in our study, it would be our contention to consider Levo-Bupivacaine as our default LA of choice in future.

Calì-Cassi *et al* showed that a decreased LoS was associated with paravertebral block.[16] Our study did not show any such significant association between LoS and type of intervention. Interestingly, a subgroup analysis showed a higher occurrence of inpatients in regional anesthesia group [Table 4]. This could be explained by the fact that major cases had a higher chance of staying overnight and a higher occurrence of major cases was noted in the regional anesthesia group.

Hypotension has been known to be associated with paravertebral, pectoral and intercostal blocks in patients who underwent mastectomy and thoracotomy.[34-36] Our study did not show any such association [Table 4]. This could be due to our study population that comprised of 'all' breast surgical cases rather than specific procedures such as mastectomies or thoracotomies.

There was no procedural complication related to the LA infiltration of wound or regional anesthesia. There was no significant association between hematoma formation and the operating surgeon. A significant higher occurrence of haematoma in the paravertebral group was noted in the current study (4 out of 21; 19%) [Table 6]. Hypotension in regional anesthesia has been thought to be due to sympathetic blockade.[36] Richard *et al* has cited hypotension during last 30 min as a risk factor for post-operative bleeding.[37] This observation certainly raises the question whether there is any correlation between regional anesthesia resulting in significant intra-operative hypotension due to sympathetic blockade and subsequent reversal of the block with return to normotension, that might lead to reactionary bleeding and formation of haematoma. Of course, we did not measure blood pressure changes specifically last 30 min of the procedure and therefore our study could not corroborate with the findings of Richard *et al*. However a significant drop in systolic blood pressure during surgery (average – lowest systolic BP) was noted in the group receiving regional block [Table 4]. Furthermore, a similar significant drop in blood pressure was also noted amongst those who received regional block and subsequently developed haematoma [Figure 2]. It could be argued that a wide variation in anesthetic practice (such as per-operative volume replacement) could have impacted on drop of BP. However only a small number (n=4) anesthetists were involved in providing most of the regional blocks, hence their practice is likely to be uniform and is unlikely to contribute to the variation in BP. Therefore, it would be worth exploring the clinical significance of haematoma in the paravertebral group, for which a larger study would be required.

In summary, regional anesthesia took longer time than LA wound infiltration, was associated with lower pain scale, and a trend of reduced morphine requirement. However, such improved patient experience has been shown to be associated with major breast procedures, than minor or moderate procedures. The outcomes were not impacted by common past medical conditions. Levo-Bupivacaine was noted to be associated with least post-operative opioid requirement (p=0.01). The study also highlighted a possible correlation between haematoma formation and paravertebral block, which would require larger studies to determine the cause-and-effect association.

We fully acknowledge the shortcomings of our study. Most importantly, this is not a randomized control trial. It is worth mentioning that observational studies can complement findings from randomized controlled trials by assessing treatment effectiveness in patients encountered in day-to-day clinical practice.[38] Moreover, the decision to offer local or regional anaesthesia depended on usual practice of the anesthetists. However, designation of anesthetists to the theatre lists was completely random. Hence it could be argued that the study entailed an in-built degree of randomization. On a positive note, the observational findings noted the study would help formulate hypotheses to be tested in future trials. Also, we admit that the relatively small numbers in the study could potentially give rise to statistical errors, which could be

mitigated by a multicentre study involving a larger number of patients.

The major strength of our study is contribution to a relatively common and yet unaddressed quandary whether one should opt for regional anesthesia in 'all' cases of breast surgery, or should a 'selective approach' be better? Furthermore, this database can be used to assess effect of regional anesthesia on long-term recurrence and survival of breast cancer in future.

Recently issued guidelines support wider use and availability of regional anesthesia. PROSPECT guidelines issued in January 2020 state 'paravertebral blockade is recommended as the first-choice regional analgesic technique. Pectoral nerves block may be used as an alternative to paravertebral block. Local anesthetic wound infiltration may be added to regional analgesia techniques.[39] Similarly, guideline from The Royal College of Anesthesiologists recommend that there should be adequate supply of regional block devices. Ultrasound scanning, nerve stimulators and all equipment and drugs necessary to perform local and regional analgesic techniques should be available.[40]

It appears that we have travelled a long way from the 'Laughing Gas' and routine 'Radical Mastectomy'. Going back to where we left in the history, Imogen, the central character in Shakespeare's Cymbeline, was noted to have had a mole in her left breast.[41] If Imogen were to have an excisional breast surgery today, should we be (or not be), based on the current evidence, offering her regional anesthesia? To be, or not to be, that remains the dilemma. We believe that our study has contributed in addressing this dilemma.

Conclusions:

In conclusion, the option of regional anesthesia should be available for all elective breast procedures. However increased theatre time should be taken into account to incorporate extra time required for regional anesthesia.

A *selective* approach involving regional anesthesia using *Levo-Bupivacaine* for *major* breast procedures would provide improved patient experience entailing lesser post-operative pain score and likely reduced post-operative morphine requirement. Common underlying health issues do not appear to have any significant impact on such an approach.

Potential association between post-operative haematoma formation in paravertebral block should be considered as a cautionary tale and warrants further evaluation.

Disclosure

The author reports no conflicts of interest in this work.

Financial support: None

References:

1. Wildsmith T. The History of Anesthesia, The Royal College of Anesthetists. Available at: https://rcoa.ac.uk/about-college/heritage/history-anesthesia. Accessed March 08, 2021
2. Robinson DH, Toledo AH. Historical development of modern anesthesia. *J Invest Surg*. 2012;25(3):141-149.
3. Sykes MK, Bunker J. Anesthesia and the Practice of Medicine: Historical Perspectives. London: Royal Society of Medicine Press Limited, 2007;28.
4. Rutkow IM. Moments in surgical history: William Stewart Halsted. *Arch Surg*. 2000;135(12):1478.
5. Ghossain A, Ghossain MA. History of mastectomy before and after Halsted. *J Med Liban*. 2009 ;57(2):65-71.
6. Jatoi I. Breast cancer: a systemic or local disease? *Am J Clin Onco*. 1997;20(5):536-539.
7. Matsumoto M, Flores EM, Kimachi PP, Gouveia FV, Kuroki MA, Barros ACSD, Sampaio MMC, Andrade FEM, Valverde J, Abrantes EF, Simões CM, Pagano RL, Martinez RCR. Benefits in radical mastectomy protocol: a randomized trial evaluating the use of regional anesthesia. *Sci Rep*. 2018;8(1):7815.
8. Rostas JW, Dyess DL. Current operative management of breast cancer: an age of smaller resections and bigger cures. *Int J Breast Cancer*. 2012;2012:516417
9. NICE guideline. Surgery for early breast cancer. Early and locally advanced breast cancer: diagnosis and treatment (2009):29. Available at: https://www.nice.org.uk/guidance/cg80. Accessed March 10, 2021
10. Tharakan L, Faber P. Pain management in day-case surgery. *BJA Education*. 2015;15 (4):180–183.
11. Tedore T. Regional anesthesia and analgesia: relationship to cancer recurrence and survival. *Br J Anesth*. 2015; 115 (S2): ii34–ii45.
12. Introduction. Blackpool Victoria hospitals NHS Foundation Trust. Available at: https://www.fyidirectory.co.uk/kb5/blackpool/directory/service.page?id=dX0Qr9RG6DM. Accessed March 10, 2021
13. Research and Development. Blackpool Teaching Hospitals NHS Foundation Trust. Available at: https://www.bfwh.nhs.uk/our-services/hospital-services/research-and-development/our-research-partners/. Accessed March 10, 2021
14. Pérez-González O, Cuéllar-Guzmán LF, Soliz J, Cata JP. Impact of Regional Anesthesia on Recurrence, Metastasis, and Immune Response in Breast Cancer Surgery: A Systematic Review of the Literature. *Reg Anesth Pain Med*. 2017;42(6):751-756.
15. Kim DH, Kim S, Kim CS, Lee S, Lee IG, Kim HJ et al. Efficacy of Pectoral Nerve Block Type II for Breast-Conserving Surgery and Sentinel Lymph Node Biopsy: A Prospective Randomized Controlled Study. *Pain Res Manag*. 2018;2018:4315931
16. Calì Cassi L, Biffoli F, Francesconi D, Petrella G, Buonomo O. Anesthesia and analgesia in breast surgery: the benefits of peripheral nerve block. *Eur Rev Med Pharmacol Sci*. 2017;21(6):1341-1345.
17. O'Riain SC, Donnell BO, Cuffe T, Harmon DC, Fraher JP, Shorten G. Thoracic paravertebral block using real-time ultrasound guidance. *Anesth Analg*. 2010;110(1):248-251.
18. FitzGerald S, Odor PM, Barron A, Pawa A. Breast surgery and regional anesthesia. *Best Pract Res Clin Anesthesiol*. 2019 ;33(1):95-110.
19. Bonica JJ and Loeser JD. 2nd Ed. The management of pain: Philadelphia: Lea and Fabiger; 1990:1046-1048.
20. Blanco R. The 'pecs block': a novel technique for providing analgesia after breast surgery. *Anesthesia*. 2011 ;66(9):847-848.
21. Blanco R, Parras T, McDonnell JG, Prats-Galino A. Serratus plane block: a novel ultrasound-guided thoracic wall nerve block. *Anesthesia*. 2013;68(11):1107-1113.
22. Haefeli M, Elfering A. Pain assessment. *Eur Spine J*. 2006;15(Suppl 1): S17–S24.
23. Wengritzky R, Mettho T, Myles PS, Burke J, Kakos A. Development and validation of a postoperative nausea and vomiting intensity scale. *Br J Anesth*. 2010 ;104(2):158-166.
24. Cancer Research UK. Breast cancer statistics. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Zero. Accessed on March 12, 2021
25. Treede RD. The International Association for the Study of Pain definition of pain: as valid in 2018 as in 1979, but in need of regularly updated footnotes. *Pain Rep*. 2018;3(2):e643.
26. Medicines Policy & Guidance Team (NHSGGC Medicines Information Service, Glasgow Royal Infirmary). Management of Post-operative Nausea and Vomiting (PONV). Available at: https://handbook.ggcmedicines.org.uk/guidelines/pain-post-operative-nausea-and-vomiting-and-palliative-care-symptoms/management-of-postoperative-nausea-and-vomiting-ponv/. Accessed March 12, 2021
27. Sinclair DR, Chung F, Mezei G. Can postoperative nausea and vomiting be predicted? *Anesthesiology*. 1999;91:109–118.
28. Bartakke AA, Varma MK. Analgesia for Breast Surgery — A Brief Overview . World Federation of Societies of Anesthesiologists (ATOTW 403):1-7. Available at: https://www.wfsahq.org/components/com_virtual_library/media/289880390b7f23adf3bd14879a3d6508-atow-403-00.pdf. Accessed March 12, 2021
29. Picard J, Meek T. Complications of regional anesthesia. *Anesthesiology*. 2010 ;65 Suppl 1:105-115.
30. Garg R, Bhan S, Vig S. Newer regional analgesia interventions (fascial plane blocks) for breast surgeries: Review of literature. *Indian J Anesth*. 2018;62(4):254–262.
31. Liguori GA, Kahn RL, Gordon MA, Urban MK. Mechanisms of hypotension and bradycardia during regional anesthesia in the sitting position. *Anesthesiology*. 2004 Jan;100(1):191-192.
32. Haller G, Courvoisier DS, Anderson H, Myles PS. Clinical factors associated with the non-utilization of an anesthesia incident reporting system. *Br J Anesth*. 2011; 107 (2):171-179.
33. Gristwood RW, Greaves JL. Levobupivacaine: a new safer long acting local anesthetic agent. *Expert Opin Investig Drugs*. 1999;8(6):861-876.
34. Skretting P. Hypotension after intercostal nerve block during thoracotomy under general anesthesia. *Br J Anesth*. 198;53(5):527-529.
35. Siddeshwara A, Singariya G, Kamal M, Kumari K, Seervi S, and Kumar R. Comparison of efficacy of ultrasound-guided pectoral nerve block versus thoracic paravertebral block using levobupivacaine and dexamethasone for postoperative analgesia after modified radical mastectomy: A randomized controlled trial. *Saudi J Anesth*. 2019; 13(4): 325–331.
36. Batra RK, Krishnan K, Agarwal. Paravertebral Block. *J Anesthesiol Clin Pharmacol*. 2011; 27(1): 5–11.
37. Richard P, Huesler R, Banic A, Erni D, Plock JA. Perioperative risk factors for haematoma after breast augmentation. *J Plast Surg Hand Surg*. 2013;47(2):130-134.
38. Silverman SL. From Randomized Controlled Trials to Observational Studies. Am J Med 2009; 122(2): 114-120. https://doi.org/10.1016/j.amjmed.2008.09.030. Accessed on March 10, 2021
39. Lemoine A, Joshi GP, Van de Velde M, Bonnet F, on behalf of the PROSPECT Working Group collaborators. PROSPECT guideline for oncological breast surgery: a systematic review and procedure-specific postoperative pain management recommendations. Anesthesia 2021 Jan 26 Available at: https://onlinelibrary.wiley.com/doi/full/10.1111/anae.14964. Accessed on March 10, 2021
40. Rockett M, Taylor J, Weiss A. Chapter 11, Guidelines for the Provision of Anesthesia Services for Inpatient Pain Management 2021. The Royal College of Anesthetists. Available at: https://www.rcoa.ac.uk/sites/default/files/documents/2020-02/GPAS-2020-11-Pain.pdf. Accessed on March 12, 2021
41. Warren R. "A note on the text". Cymbeline. Manchester, UK: Manchester University Press 1989: p. viii.