GHANA COLLEGE OF PHYSICIANS AND SURGEONS

FACULTY OF ANAESTHESIA

PERIOPERATIVE ANALGESIC EFFECT OF SERRATUS ANTERIOR PLANE BLOCK ON BREAST SURGERY.
A PROSPECTIVE, RANDOMIZED, CONTROLLED DOUBLE BLIND STUDY CONDUCTED AT THE KORLE BU TEACHING HOSPITAL, ACCRA, GHANA.

A BOOK OF DISSERTATION SUBMITTED TO THE FACULTY OF ANAESTHESIA, IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE CONFERMENT OF A FELLOW OF THE GHANA COLLEGE OF SURGEONS (FGCS).

BY

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DECLARATION

I, David Kofi Mensah, hereby declare that the content of this dissertation is my own work carried out under supervision, except where due acknowledgement is made in the text. This study has not been submitted to any other college for a fellowship.

…….

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STRUCTURED ABSTRACT

INTRODUCTION

Breast cancer is the most common cancer in women both in the developed and less developed world, according to World Health Organisation. The mainstay of treatment for breast cancer is breast surgery. Pain after breast surgery has been described as moderate to severe. Inadequately treated post-operative pain after breast surgery invariably leads to greater postoperative morbidity, higher hospital cost and persistent post-operative pain. Opioids have been the drugs of choice for management of postoperative pain after breast surgery, however, they are associated with many undesirable side effects. Serratus anterior plane (SAP) block is a new interfascial injection technique for analgesia of the chest wall. There is paucity of data with regards to its use for pain relief and possible opioid-sparing in the West Africa subregion.

AIM

The aim of this study was to determine whether serratus anterior plane block administered for breast surgery has analgesic effect during the perioperative period in patients undergoing elective breast surgery at the Korle-Bu Teaching Hospital.

METHODOLOGY

This was a prospective, randomized, double-blinded study. Following Ethical Committee approval, patients who fulfilled the inclusion criteria and gave informed consent were consecutively enrolled into the study. A total of fifty-two (52) patients were enrolled into the study and were randomly assigned into one of two groups. The intervention group (n=26) and the placebo group(n=26). Patients demographic characteristics were recorded. Their pre-induction blood pressure, heart rate, respiratory rate and oxygen saturation were also noted. All patients underwent standard general anaesthesia and their airways secured with laryngeal mask airways. After induction of anaesthesia a blinded anaesthetist performed ultrasound guided serratus anterior plane block with 0.25% plain bupivacaine or 0.9% normal saline. Intraoperatively, heart rate and mean arterial blood pressure were maintained within 20% of the preoperative baseline values by giving intravenous bolus doses of morphine. Intraoperatively, patients' blood pressure, heart rate and respiratory rate were recorded every five minutes. After surgery, a blinded investigator assessed and noted the numerical rating scale (NRS) score of pain at the recovery ward when patients were conscious and alert, at 1, 4, 8 and 24 hours postoperatively. The incidence of PONV was recorded immediate postoperative

period and at 1, 4, 8 and 24 hours postoperatively. Patient satisfaction was also assessed using a simple questionnaire.

RESULTS

Patients receiving SAP block had lower NRS scores at all measured time points but this was only statistically significant at 4 hours postoperative time(*p-value*=0.002).

The mean intraoperative opioid consumed (morphine equivalent) was slightly higher in the control group (11.9±1.5mg) than it was in the intervention group(11.3±1.5mg), however the difference was not statistically significant (*p value* = 0.131)

There was statistically significant difference in the postoperative opioid consumption in the intervention group and the control group (4.6±5.7mg versus 10.5 ± 6mg) respectively (*p value*=0.001).

Most participants in this study did not experience PONV. Those who had PONV, the highest incidence occurred 4 hours postoperatively but this was not statistically significant between the two groups (p-value = 0.098). No participant experienced severe PONV. No adverse effects were noticed in those who had the SAP block.

Generally, patients in both groups were very satisfied with their postoperative pain management.

CONCLUSION

Serratus anterior plane block reduces NRS pain scores postoperatively. It also significantly reduces postoperative opioid consumption but does not significantly reduce intraoperative opioid consumption.

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LIST OF ABBREVIATIONS

AAGBI	Association of Anaesthetists of Great Britain and Ireland
ALND	Axillary lymph node dissection
ASA	American Society of Anaesthesiologist
BMI	Body-mass index
CAS	Colour Analogue Scale
CNS	Central nervous system
CTZ	Chemoreceptor trigger zone
DBP	Diastolic blood pressure
DCIS	Ductal carcinoma in situ
DN4	Douleur Neuropathique en 4
ESPB	Erector spinae plane block
FPS-R	Faces Pain Scale Revised
HER2	Human epidermal growth factor 2
HR	Heart rate
IASP	International Association for the Study of Pain
IV	Intravenous
KBTH	Korle Bu Teaching Hospital
LAST	Local anaesthetic system toxicity
MAC	Minimum alveolar concentration
MAP	Mean arterial pressure
MRM	Modified radical mastectomy
NIBP	Non- invasive blood pressure
NRS	Numerical Rating Score
NSAIDS	Non-steroidal anti-inflammatory drugs
PACU	Post Anaesthesia Care Unit
PBI	Pain Burden Index
PEC	Pectoralis
PMPS	Post mastectomy pain syndrome
PONV	Postoperative nausea and vomiting
RCT	Randomized control trial
RR	Respiratory rate
SAPB	Serratus anterior plane block

SBP	Systolic blood pressure
SPSS	Statistical Package for Social Sciences
VAS	Visual Analogue Scale
GRS	Graphic Rating Scale
VRS	Verbal Rating Scale
WLE	Wide local excision

CHAPTER 1: INTRODUCTION

1.1 Introduction

Breast cancer is a major public health problem worldwide. It is the most common cancer in women, comprising approximately 11% of all cases.[1] Management is multidisciplinary and usually involves a combination of surgery, radiotherapy and chemotherapy.[2] For the majority of breast cancer cases, surgery is the primary and most effective therapeutic intervention.[3] According to Cancer Research UK one in eight women will develop breast cancer of which approximately 81% will be treated with mastectomy with or without reconstruction.[4] Breast surgery is an integral part of management of breast cancer and it covers a wide range of procedures such as lumpectomies, mastectomy with axillary clearance and reconstruction.

Mastectomy is the mainstay of treatment for patients with breast cancer at the study site .[5] This surgery causes significant pain and may progress to chronic pain states in 25-60% of cases.[6] Many women who undergo breast surgery suffer from ill-defined pain syndromes. It is believed that there is even significant postoperative pain following minor procedures.[7]

There are several ways of managing pain after breast surgery.[8] Commonly used systemic medications are non-steroidal anti-inflammatory drugs(NSAIDS) and opioids, however, NSAIDS are associated with impaired renal function and haemorrhagic disorders.[9] Also, there are many undesirable side effects of opioids such as nausea and vomiting, constipation and respiratory depression.[10] This has resulted in increased interest in regional anaesthesia for breast surgery, including techniques such as thoracic paravertebral, thoracic epidural and peripheral nerve blocks.[11] Commonly used techniques such as thoracic epidural blocks and paravertebral block have complications that make them unsuitable for day surgery.[12]

Ultrasound-guided serratus anterior plane block has recently been described as a regional anaesthetic technique to provide analgesia for breast and thoracic wall surgeries.[13] It has rapidly gained popularity in breast surgery due to its relative simplicity, safety and perceived efficacy.[14] Serratus anterior plane block provides analgesia to the anterolateral chest wall by blocking the lateral branches of the intercostal nerves .[13] It is a technically simple block and can be safely performed as a bedside procedure.

This study sought to find out if serratus anterior plane block would be a good alternative regional anaesthesia technique for patients coming for breast surgery and if it would reduce perioperative opioid use in these patients.

1.2 Problem statement

Despite the latest advances in breast cancer surgery, this procedure is frequently associated with significant postoperative pain, nausea and vomiting, which lead not only to increased patient suffering, but also to a prolongation of hospital stay and related costs.[15] Opioids which are commonly used to manage postoperative pain after breast surgery have many deleterious effects.[10] Thoracic paravertebral nerve block offers benefits enhancing surgical anaesthesia and postoperative analgesia therefore considered a viable option to the classic multimodal analgesia.[16] However it is technically more difficult to perform, it is associated with serious side effects such as epidural, subdural or intrathecal injection of local anaesthetics and is therefore not routinely offered to patients at the Korle Bu Teaching Hospital (KBTH). Breast cancer surgery is associated with moderate to severe pain during the early postoperative period, however postoperative pain management is sub-optimal from unpublished data at the study site. Therefore, it has become necessary to look for a good regional anaesthetic alternative, such as serratus anterior plane block, that is equally effective and can easily be performed with lower complication rates.

1.3 Justification/Relevance

Persistent pain after breast surgery continues to have a high prevalence.[4] This is associated with reduced quality of life. However this can be lessened if optimal perioperative analgesia technique is instituted.[17]A study at the research site by Clegg-Lamptey et al revealed that postoperative pain amongst surgical patient is mainly managed with pethidine and the results are unsatisfactory.[18] Therefore there is the need to look for a regional block which is simple and easy to perform but very effective. In the wake of the opioid menace, an opioid sparing modality such as serratus anterior plane block in KBTH will go a long way to help both patients and doctors. The outcome of this study may help change protocols to offer the best available pain relief technique to patients coming for breast surgery at the study site.

1.4 General Objective

The general objective of this study was to determine the perioperative analgesic effect of serratus anterior plane block in patients undergoing elective breast surgery in Korle Bu Teaching Hospital.

1.5 Specific Objectives

The specific objectives of this study were to determine in patients coming for elective breast surgery at the Korle Bu Teaching Hospital (KBTH), the following:

1. The demographic characteristics of patients.
2. The incidence and severity of postoperative pain in those receiving a SAP block with bupivacaine versus those receiving placebo.
3. The intraoperative and postoperative analgesic effect of SAP block.
4. The total amount of opioid (morphine equivalent) required in the first 24 hours in those receiving a SAP block with bupivacaine versus those receiving placebo.
5. The numerical rating scale (NRS) score of patients at 1, 4, 8 and 24 hours postoperatively.
6. The incidence of postoperative nausea and vomiting (PONV).
7. The level of patient satisfaction with postoperative analgesia in those receiving a SAP block with bupivacaine versus those receiving placebo.

CHAPTER 2: LITERATURE REVIEW

2.1 Anatomy of the Breast

The breasts are paired structures located on the anterior thoracic wall, in the pectoral region. They are the most superficial aspect of the anterior chest wall and are present in both males and females yet, are more prominent in females following puberty. Many studies have found that women's breasts are more asymmetric than men's.[19]

They are found anterior to the deep fascia and pectoral muscles; separated from them by the retromammary space. In young adults, the skin directly over the breast tissue is characterized by a nipple areola complex that is centrally positioned.[20]

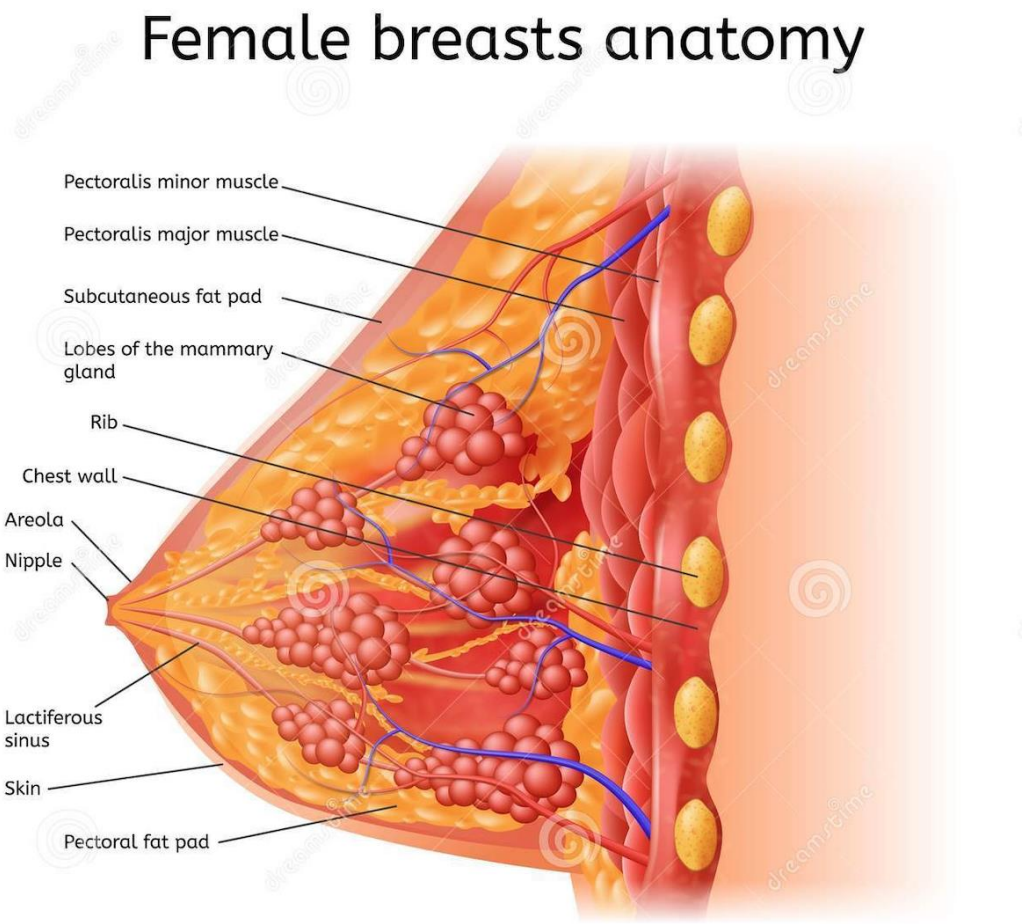

Figure 2.1: Anatomy of the female breast

(Source:dreamstime.com)

The borders of the breast are the second intercostal space superiorly, the midaxillary line laterally, the inframammary line inferiorly, and the sternum medially. The breasts lie over the pectoralis muscle, serratus anterior muscle and uppermost portion of the rectus abdominis muscle between the second and sixth ribs.[20,21]

Embryogenesis

Around the sixth week of gestation, the breasts begin to grow. Around the seventh week, the milk line shows as a distinct linear elevation. The rudimentary breast forms from the thicker white line at the end of the eighth week and will eventually become the mature breast. The proliferation of basal cells occurs throughout development. The nipple emerges at about 38 to 40 weeks of gestation.[20,21]

The majority of the breast consists of glandular (milk-producing) and fatty tissues. The mammary glands are modified apocrine sweat glands and are ectodermal in origin. The ratio of fat versus glandular tissues varies among individuals. It depends on genetics, age, post-menopausal, post-partum, or pregnancy status. The gland is comprised of 15-20 secretory lobes which are separated by fibrous bands called the suspensory ligaments of the breast (of Cooper). [22]

The non-ptotic shape of the breasts is supported by these ligaments, which originate from the underlying thoracic fascia and insert into the dermis of the overlying skin. The secretory lobes contain numerous lobules comprised of the tubuloalveolar glands. The secretory ducts of the lobes, called the lactiferous ducts, converge and open onto the nipple.[21]

The nipples are surrounded by a pigmented circular region of skin called the areola, which becomes even more pigmented and prominent during puberty. The numerous areolar glands cause little punctual elevations on the surface of the areola. These are mostly sweat and sebaceous glands, as well as the modified mammary glands called the glands of Montgomery. Their function is to produce an antimicrobial secretion that protects the surface of areola.[21]

Blood supply and lymphatics

The breast skin receives its blood supply from the subdermal plexus; these tiny blood vessels, in turn, communicate with deep underlying arterioles which supply the breast parenchyma. Blood is supplied to the breast from the following vessels:

- The thoracoacromial artery
- Internal mammary perforators (second to fifth)
- Lateral thoracic artery
- Thoracodorsal artery
- Terminal branches of the intercostal perforators (third to eighth)

Overall, at least 60% of the blood supply is from the superomedial perforators which come off the internal mammary artery.

The breast also has profuse venous drainage divided into the superficial and deep veins. The superficial veins are found along the anterior surface of the fascia; these veins follow the areola path under the nipple areolar complex, often referred to as the venous plexus of Haller. Deep inside the breast are many large veins which drain into the chest wall veins.[23]

The breast also has extensive lymphatic drainage that runs both superficially and deep within the breast. The superficial lymphatics are the areolar and subareolar plexus. The latter also receives lymphatics from glandular tissues. The superficial lymphatics continue posteriorly and medially and eventually reach the axillary lymph nodes.[23]

Sensory innervation

The thoracic wall is innervated primarily by the intercostal nerves, which are the ventral rami of spinal nerves of T1-T11 and the ventral ramus of T12(subcostal nerve). The ventral ramus of T1 also forms the lower trunk of the brachial plexus. Each intercostal nerve supplies a dermatome and a myotome.[24]

These nerves enter the medial-most parts of the posterior intercostal spaces. Initially, they run within the endothoracic fascia just between the parietal pleura and the internal intercostal membrane. Near the angle of the ribs, the nerves pass between the internal intercostal and the

innermost intercostal muscles. They continue to course inferior to the costal grooves running inferior to the intercostal arteries.[25]

The nerves continue anteriorly between the internal and innermost intercostals and supply these muscles and other muscles and give rami communicants to the sympathetic trunks.
At the midaxillary line they give rise to lateral cutaneous branches which goes through the muscles of the lateral thoracic wall and then divide into anterior and posterior branches to give cutaneous information from the skin of the lateral thoracic wall.[25]

The anterior cutaneous branch is the terminal branch of the typical intercostal nerves and divides into medial and lateral branches to supply the skin of the anterior thoracic wall.[26] The anterolateral and anteromedial branches of the thoracic intercostal nerves T3–T5 provide dermatomal sensory innervation to the breast. The supraclavicular nerves, which emerge from the cervical plexus, supply the upper and lateral regions of the breast. The lateral cutaneous branch of the T4 intercostal nerve is primarily responsible for sensory innervation of the nipple.[27]

The pectoralis major and minor muscles are innervated by the lateral and medial pectoral nerves; the serratus anterior is innervated by the long thoracic nerve and the latissimus dorsi is innervated by the thoracodorsal nerve. [25]These nerves are branches of the brachial plexus.

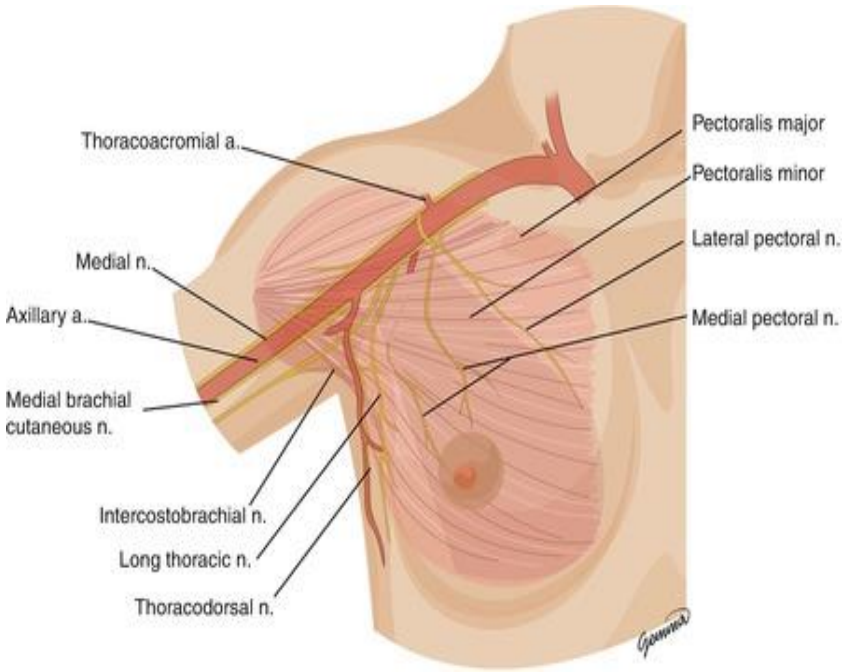

Figure 2.2: Innervation of the chest wall muscles

(Source:link.springer.com)

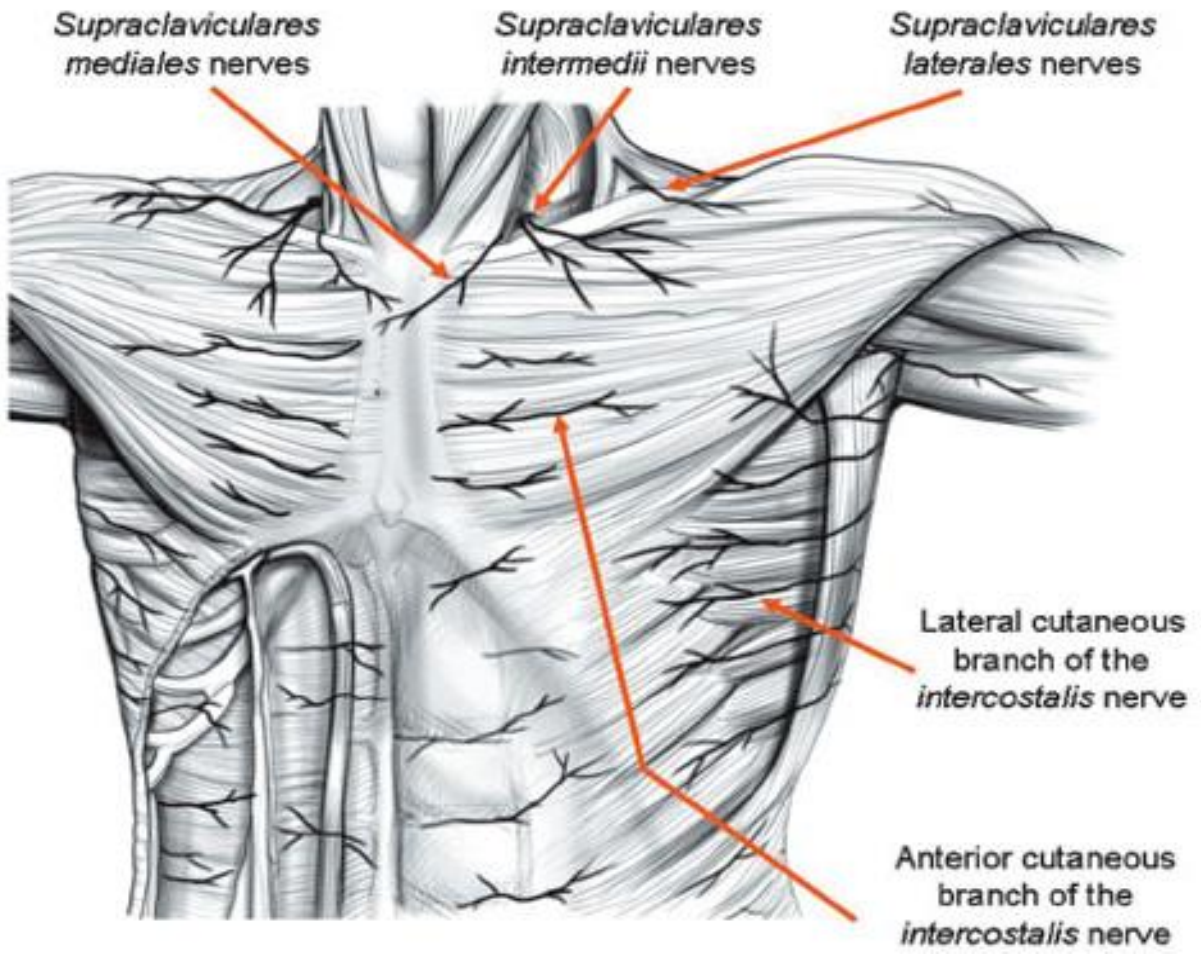

Figure 2.3: Innervation of the breast

(Source:researchgate.net)

2.2 Breast surgery

Breast surgery is a broad term that refers to a variety of operations. These procedures range from breast conserving surgery to mastectomy to specialized oncoplastic techniques and reconstructive procedures.[28]

Although surgery remains important in the treatment of breast cancer, there has been a progressive shift toward more conservative approaches, which has been backed up by clinical trials that have shown that mastectomy and local excision followed by radiotherapy are equally effective.[29]

Breast lump excisions are classified as either local(lumpectomy) or wide local excisions. Lumpectomy involves removal of only the lump. This is an effective method for removing benign lesions. Wide local excision of breast lump involves the removal of the lesion together with a border of macroscopically normal breast tissue. This is gradually becoming the primary surgical treatment in proven, and occasionally suspected, early breast cancer.[30]

Invasion beyond the primary tumour may expand to the margins of the excision, necessitating a later, more radical local excision or mastectomy. If this is the case, the incision should be made within the ellipse of skin that will be removed later.[30]

The goal should be to achieve a decent cosmetic effect. Circumferential incisions are superior to radial incisions in terms of scarring. Incisions in the breast's superomedial quadrant frequently result in hypertrophic scars in a cosmetically sensitive area, hence they should be avoided if at all feasible.[30]

Mastectomy on the other hand are indicated for large tumours in relation to the size of the breast, central tumours beneath or involving the nipple, multifocal disease, local recurrence or patient preference.[31] Initially, Halsted's radical mastectomy was accepted as the standard of care for breast cancers. This included excision of the breast, axillary lymph nodes and pectoralis major and minor muscles. It was associated with significant morbidity with no overall survival benefit therefore hardly performed these days. To reduce morbidity, Patey introduced the modified radical mastectomy (MRM) which involves removal of the breast, pectoralis major fascia, and level I and II axillary lymph nodes.[32]

Simple mastectomy comprises excision of only the breast with no dissection of the axilla, except for the region of the axillary tail of the breast which sometimes has few nodes low in the anterior group attached to it. [29] An elliptical skin incision is used to remove the entire breast, nipple, and areola in as shown in figure 2.4 .The skin is incised and the incision deepened through the subcutaneous fat. The top and lower flaps are raised until the plane comes down to the deep fascia at the margin of the breast. The breast is next dissected from above downwards from the deep fascia, and all bleeding vessels are clamped. The dissection of the axillary tail is continued into the axilla when the lateral margin of the pectoralis major is reached.[30]

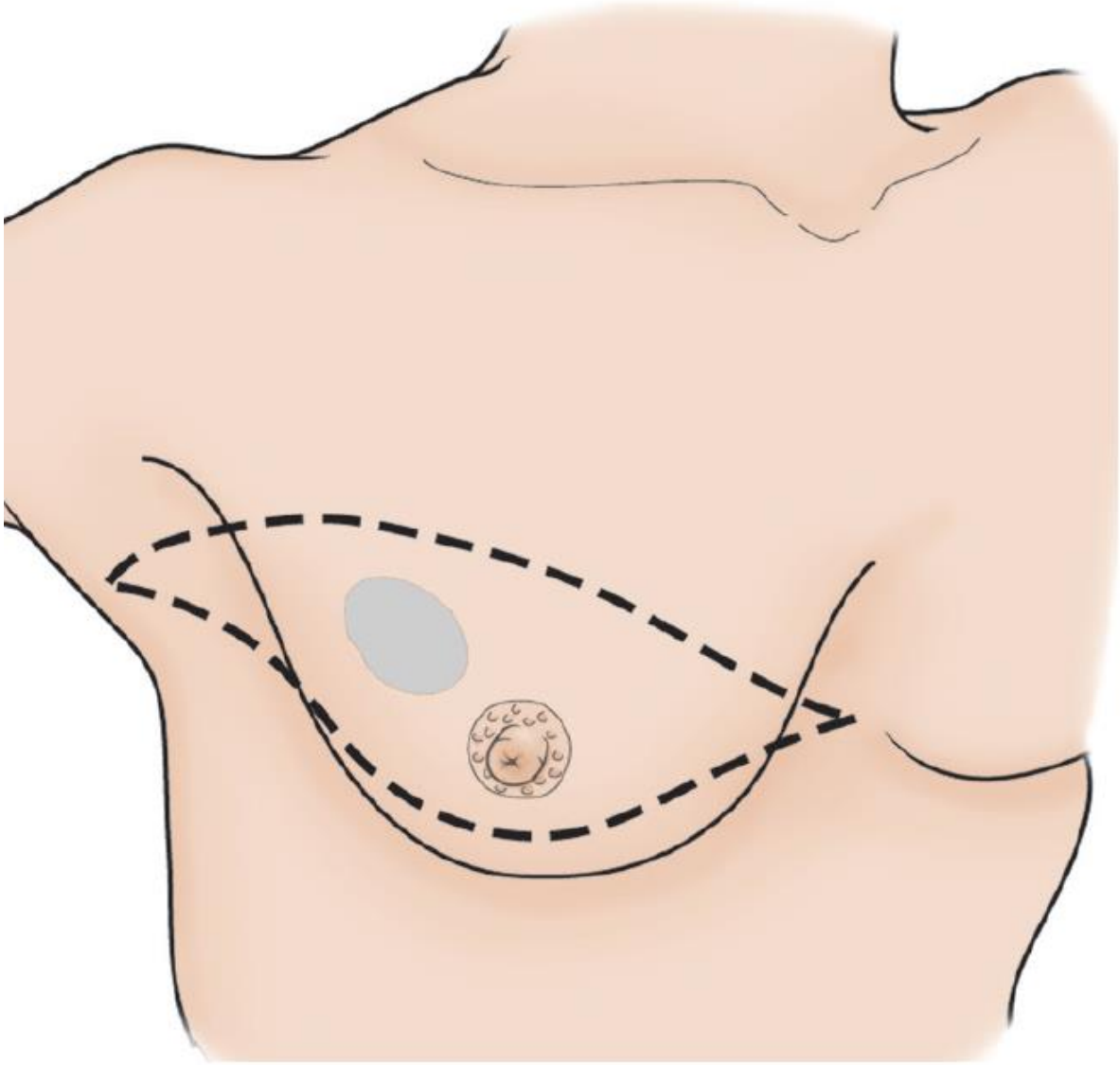

Figure 2.4: A right simple mastectomy - a slightly oblique elliptical skin incision is made

(Source: Farquharson's Textbook of Operative Surgery, 10th Edition)

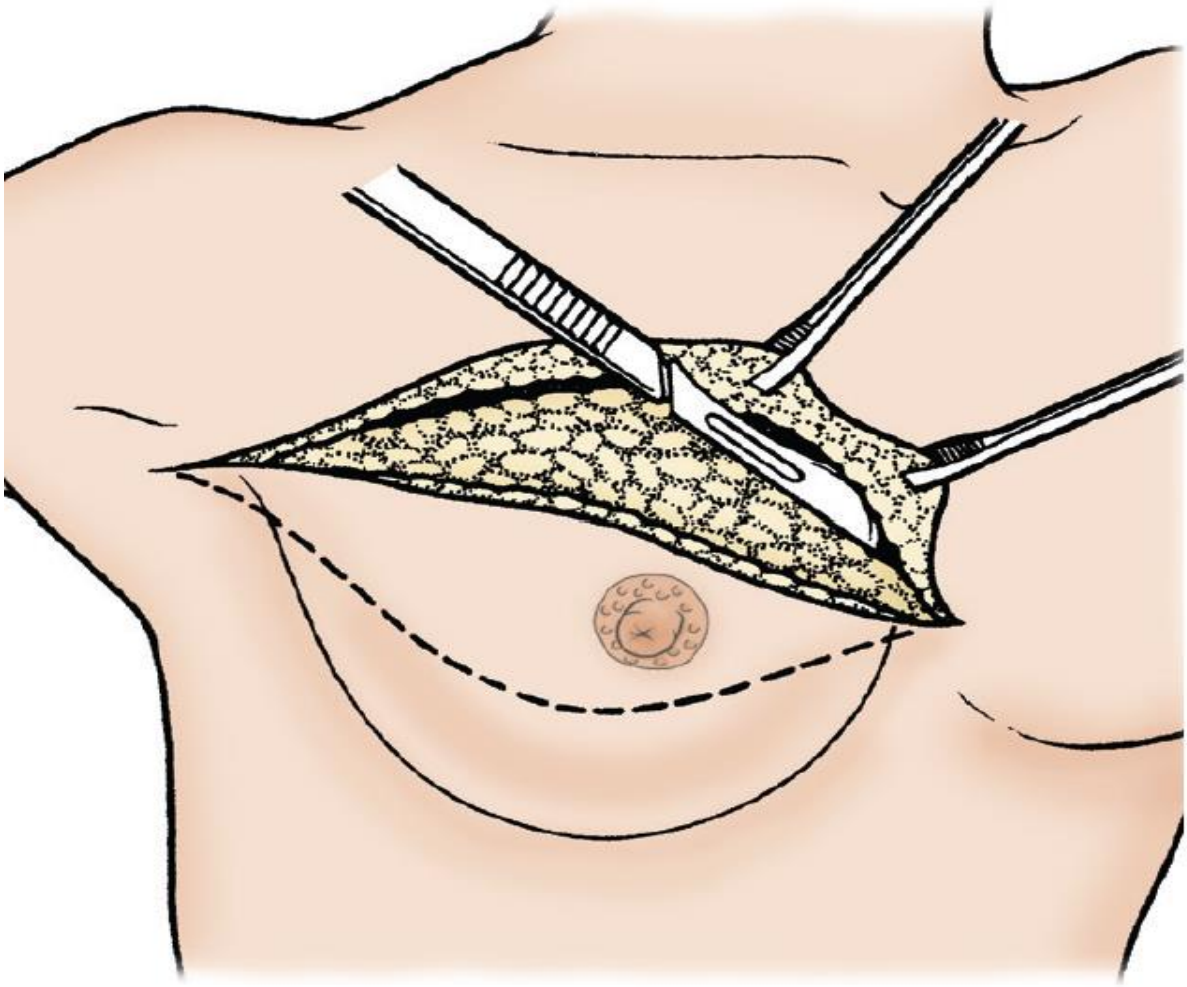

Figure 2.5: Dissection of the upper skin flap – the natural plane between subcutaneous fat and breast tissue is followed

(Source: Farquharson's Textbook of Operative Surgery, 10th Edition)

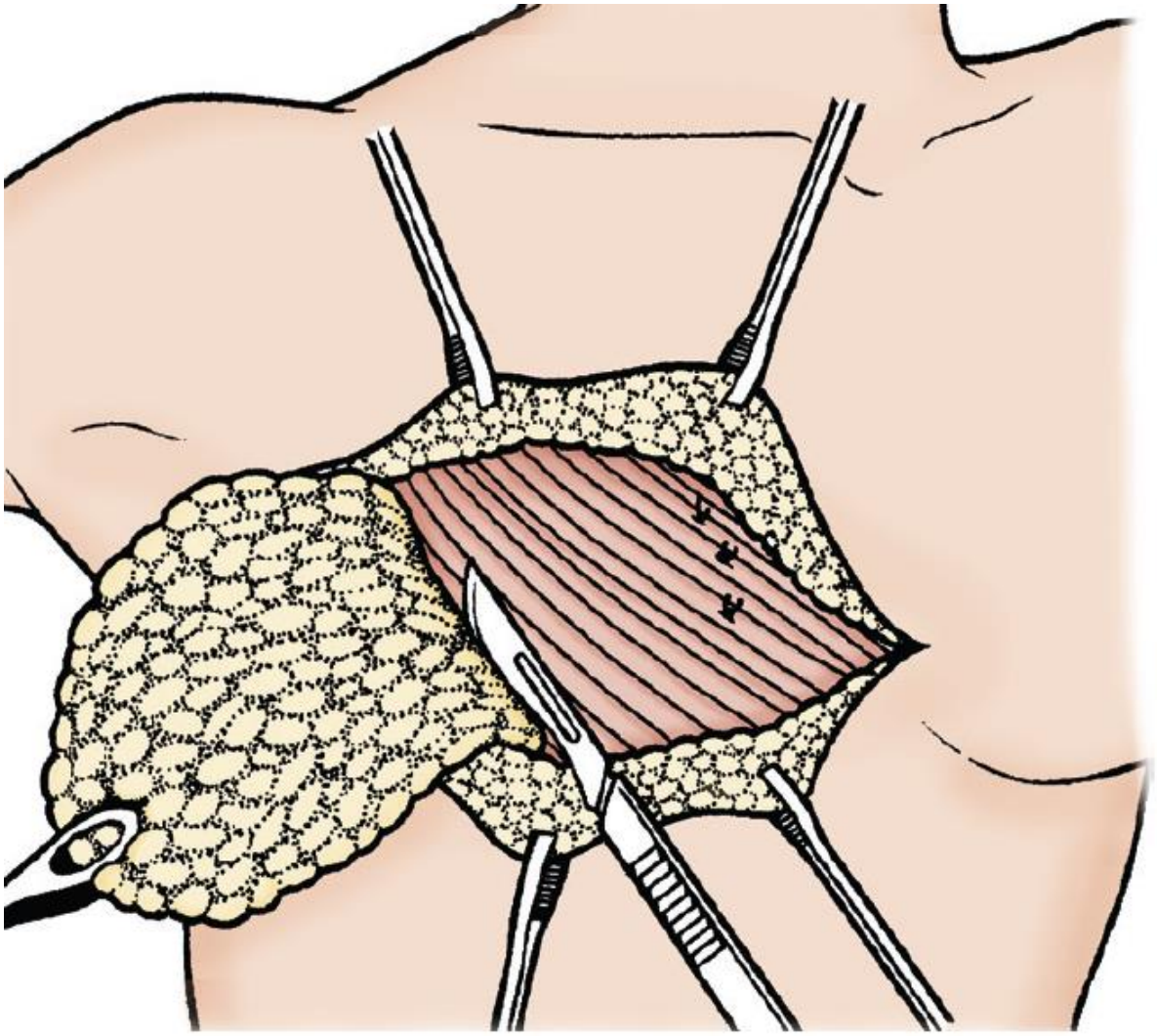

Figure 2.6: Dissection of the breast off the deep fascia from above downwards

(Source: Farquharson's Textbook of Operative Surgery, 10th Edition)

Metastasis to the axillary lymph nodes is an important prognostic factor in breast cancer. Nodal spread influences surgical and adjuvant treatment. [28] The pectoralis minor muscle is the landmark used to classify the lymph nodes in the axilla. Level I lymph nodes are lateral to and below the pectoralis minor muscle, level II lymph nodes are found behind the muscle and level III lymph nodes are above and medial to it. [30] The role of axillary surgery is to stage the patient and to remove metastatic disease within the lymph nodes.[33] In the past, all patients who had mastectomy had axillary lymph node dissection irrespective of their nodal status. Recently a more conservative approach to the axilla has been adopted.[28] Traditionally all 3 levels of axillary nodes were removed but recently mostly level 2 clearance is performed. This involves removal of level I and II lymph nodes. More recently, a new procedure known as a sentinel

node biopsy has been introduced, in which a specific lymph node draining the tumour is excised after being labelled with a radio isotope and stained with a blue dye.[34]

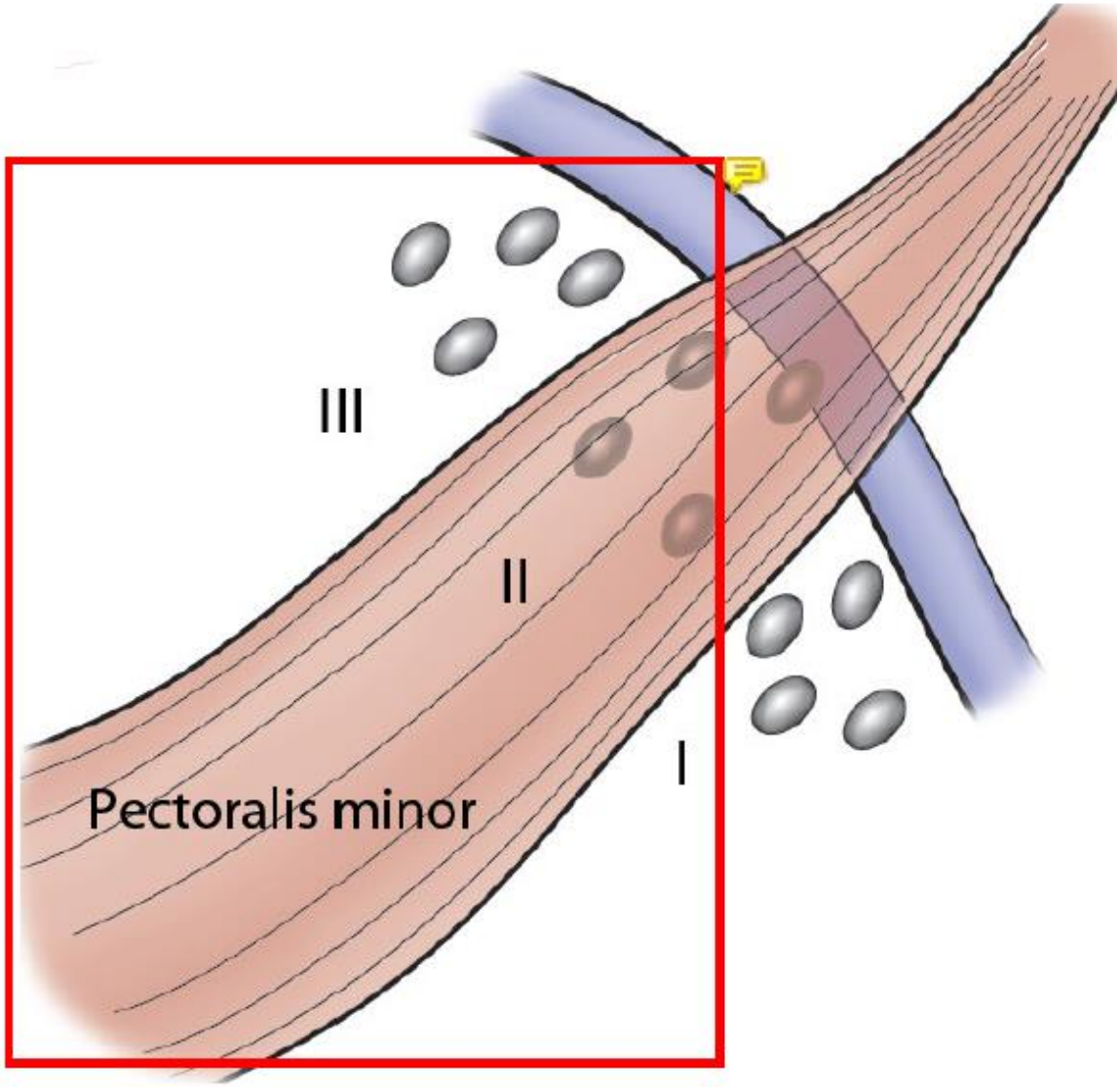

Figure 2.7: Axillary lymph node classification: level I (below and lateral), level II (behind) and level III (above and medial) to the pectoralis minor muscle

(Source: Farquharson's Textbook of Operative Surgery, 10th Edition)

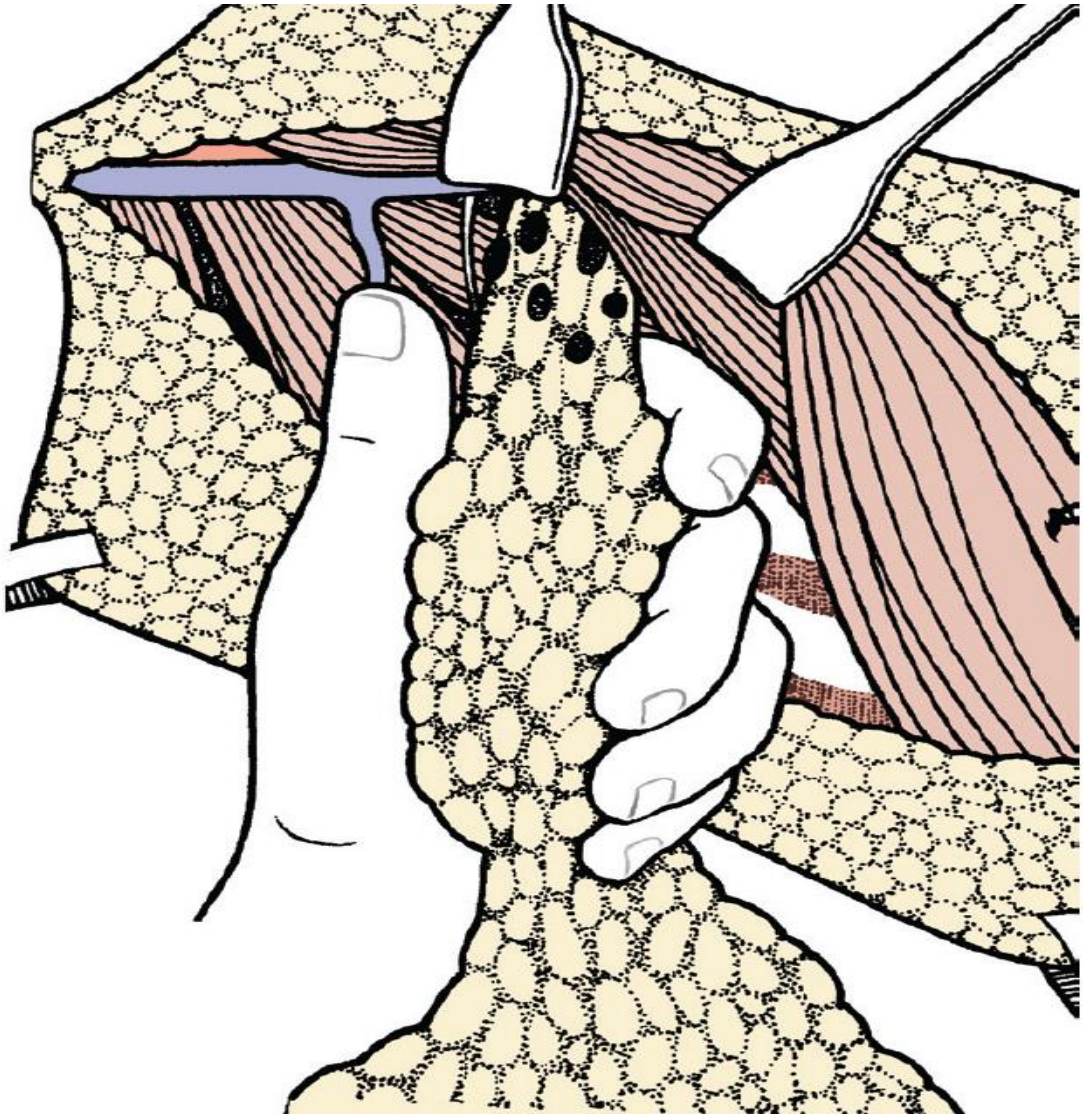

Figure 2.8: Axillary lymph node dissection

(Source: Farquharson's Textbook of Operative Surgery, 10th Edition)

2.2.1 Oncoplastic Surgery and Reconstruction

The primary goal of breast cancer surgery is complete removal of the tumour. However, aesthetically pleasing breast reconstruction can have a significant impact on the patient's quality of life. [35] There are different types of oncoplastic surgery, however, the location of the cancer within the breast determines which procedure to employ. Skin sparing mastectomy was one of the early oncoplastic procedures used for DCIS because of its excellent cosmetic outcomes and good oncological profile. It involved excision of the breast parenchyma whiles sparing most of the breast skin. [36]Another commonly performed procedure is the nipple sparing

mastectomy. This procedure preserves the nipple alveolar complex whiles removing all the major ducts within the nipple lumen. It is mainly carried out for high risk women undergoing prophylactic mastectomy.[36] Breast reconstruction can be performed using several techniques including an expander/implant and/or autologous tissues. The commonest breast reconstruction performed after mastectomy is the latissimus dorsi musculocutaneous flap.[28] After a mastectomy and axillary dissection, the patient is turned on the side and an appropriate sized ellipse is marked on the latissimus dorsi muscle. The skin is incised, leaving the ellipse attached to the underlying latissimus muscle.[30]

To expose the muscle's borders, skin and fascia are dissected from the muscle proximal and distal to the skin ellipse. Deep dissection starts at the anterior border and proceeds medially and inferiorly. The medial attachment to the thoracodorsal fascia is divided carefully, continuing cranially. The upper border is then delineated and dissected above and lateral to the latissimus dorsi tendon and towards the angle of the scapula. Deep dissection is then continued, with special attention paid to the thoracodorsal vessels and the serratus anterior muscle artery which influence flap viability. After that, the flap pedicle is dissected until it can be twisted and transferred subcutaneously along the chest wall to fill the breast defect.[30]

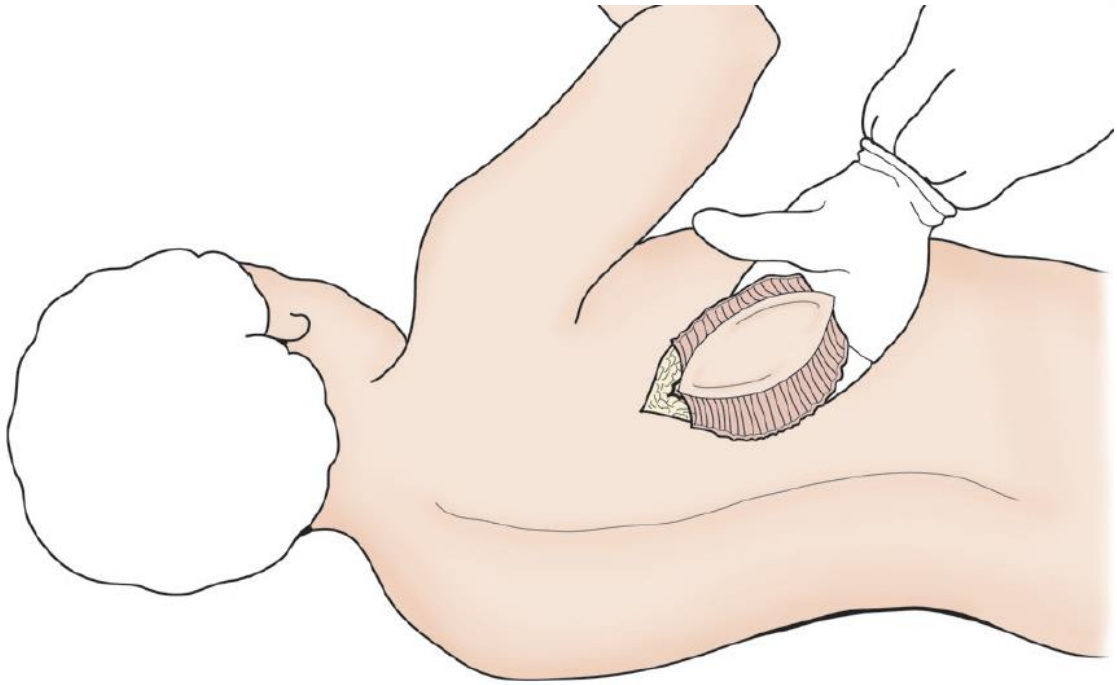

Figure 2.9A right latissimus dorsi reconstruction. (a) An ellipse of skin just below the scapula is raised with its underlying portion of latissimus dorsi

(Source: Farquharson's Textbook of Operative Surgery, 10th Edition)

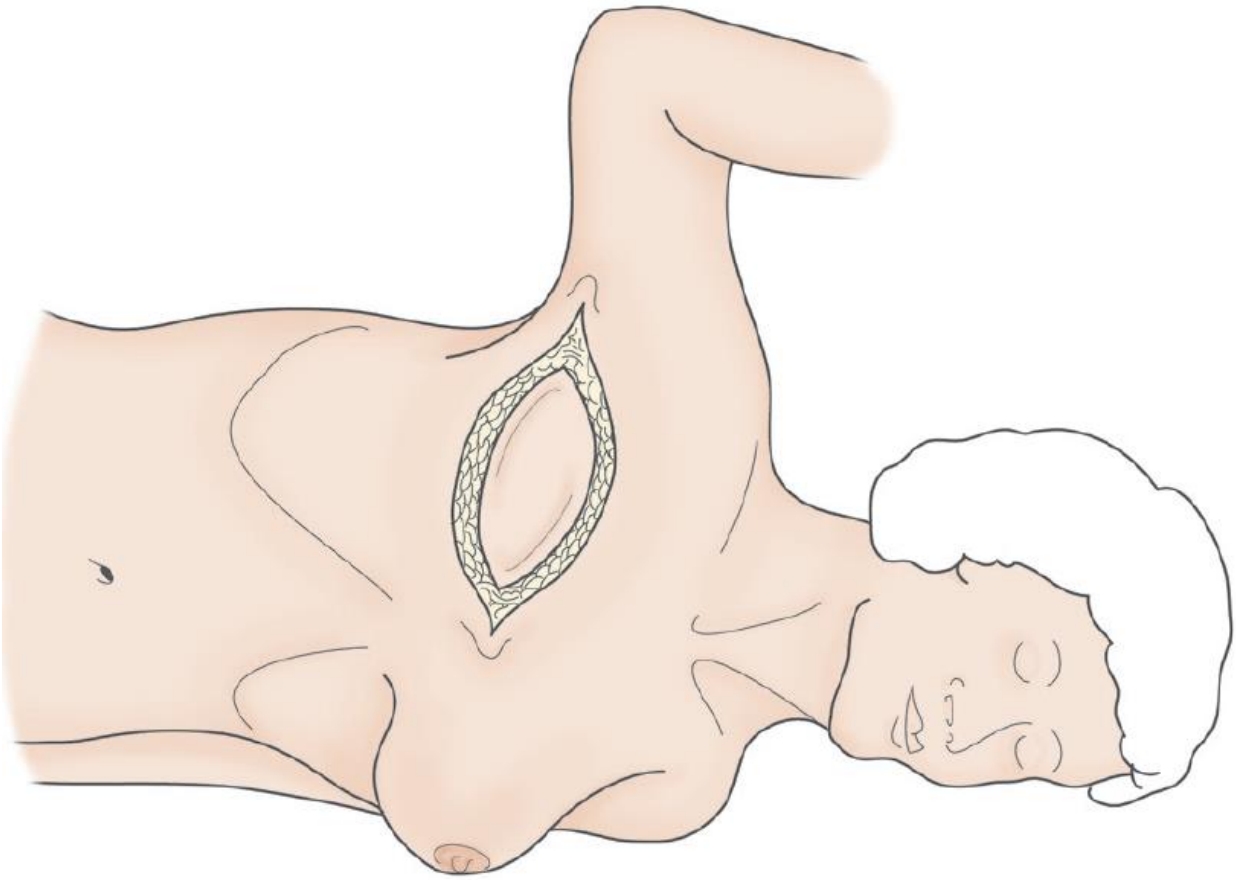

Figure 2.10: A latissimus dorsi reconstruction. (b) The myocutaneous flap is rotated and tunnelled subcutaneously into the mastectomy wound defect

(Source: Farquharson's Textbook of Operative Surgery, 10th Edition)

Breast cancer in its early stages is thought to be curable, metastatic breast cancer on the other hand has a very poor prognosis. The cause of breast cancer still remains unclear. Most women develop breast cancer with no identifiable risk factors. Hereditary causes account for only 5-10% of cases, while germline mutations in breast cancer gene(BRCA)1 or BRCA2 account for 30% of inheritable breast cancer cases.[37]

Non-hereditary risk factors include early menarche, late age at menopause, exogenous hormone intake, alcohol consumption, smoking, and obesity. There are different biological subtypes of breast cancer based on the status of hormone receptors (estrogen and progesterone receptors) and expression of HER2. The common biological subtypes are luminal A, luminal B, human epidermal growth factor receptor 2(HER2)-positive, and triple-negative breast cancer.[38]

In spite of the advances made in the diagnosis and treatment of breast cancer, different countries develop at different speeds in the management of the disease, leading to diversity of disease burden.[39]

Global Cancer Statistics 2020 estimates that breast cancer in females represents 11.7% of all cancer cases with an estimated 2.3 million new cases. It has now surpassed lung cancer as the leading cause of global cancer incidence in 2020. It is the 5th leading cause of cancer death worldwide.[40]

Incidence rates of breast cancer are 88% higher in transitioned countries than in transitioning countries (55.9 and 29.7 per 100,000, respectively). The highest incidence rates(>80 per 100,000) can be found in Australia/New Zealand, Western Europe (Belgium has the world's highest incidence), Northern America, and Northern Europe. Central America, Eastern and Middle Africa, and South Central Asia have the lowest incidence rate(<40 per 100,000).[40]

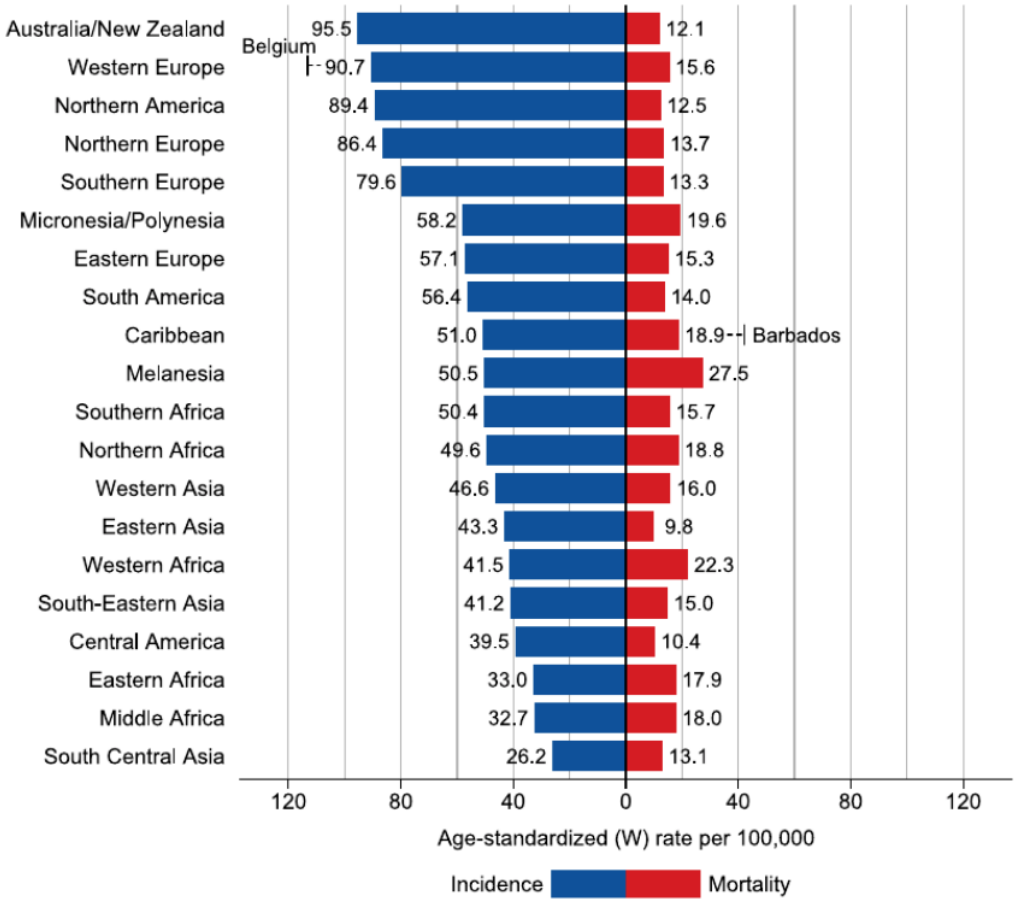

Figure 2.11: Region-Specific Incidence and Mortality Age-Standardized Rates for Female Breast Cancer in 2020

(Source: GLOBOCAN 2020)

Although incidence rate in transitioning countries is lower, women living in these countries have 17% higher mortality rates compared with women in transitioned countries (15 and 12.8 per 100,000 respectively). The highest mortality rates are recorded in Western Africa, Melanesia , and the Caribbean.[40]

It is also noted that the incidence rate in transitioning countries is on the rise and this can be attributed to growing economy and the adoption of western lifestyle. This has resulted in a convergence towards the risk factor profile of Western countries-postponing childbearing and having fewer children, higher levels of excess body weight and physical inactivity.[40]

Sub-Saharan Africa is experiencing a rapid rise in incidence rate. Between the mid-1990s and the mid-2010s, incidence rates increased by >5% per year in Malawi , Nigeria, and the Seychelles and by 3% to 4% per year in South Africa and Zimbabwe.[40] Mortality rates in Sub-Saharan African regions have risen at the same time and currently rank among the highest in the world, indicating a lack of health infrastructure and, as a result, poor survival rates.[40] In 12 Sub-Saharan African nations, 5-year age-standardized relative survival was 66 percent for cases detected between 2008 and 2015, compared to 85 percent to 90 percent for cases diagnosed in high-income countries between 2010 and 2014.[40]

In Ghana, a cancer registry conducted at Kumasi estimates the highest cause of cancer among females to be breast cancer at an incidence rate of 34%.[41]At the Korle Bu Teaching Hospital, Calys-Tagoe et al found out that breast cancer was the most common form of cancer seen in the hospital with a prevalence of 80.5 cases per 100,000 hospital attendees.[42] Studies by Clegg-Lamptey et al in 2009 showed a rise in breast cancer cases in Ghana. Breast cancer now accounts for 16% of all cancers in Ghana.[5] This observation is consistent with studies carried out in other Sub-Saharan African countries.[43] There are different management strategies of breast cancer depending on the stage of presentation of the disease.[44] The standard treatment options for early, localized , or operable breast cancer may include breast-conserving surgery and sentinel node biopsy with or without axillary lymph node dissection. Another option is radical mastectomy with or without breast reconstruction and sentinel node biopsy with or without axillary lymph node dissection for positive sentinel lymph nodes.[45]In Ghana, more than 50% of the patients present with advanced disease therefore are managed with chemotherapy and surgery.[46,47] The theatre record books at the Korle Bu teaching hospital in 2018 revealed that elective breast surgery constituted 10.1% of all elective general surgical procedures. These surgeries are usually performed under general anaesthesia.

2.3 Morbidity associated with breast surgery

The breast is considered a clean organ and has no direct connection to any major body cavity or visceral structures; thus, most breast operations are considered as low-morbidity procedures. However, there are some commonly recognized morbidities associated with breast surgeries such as moderate to severe postoperative pain , postoperative nausea and vomiting (PONV) and brachial plexopathy.[48]

2.3.1 Acute postoperative pain

As a result of early diagnosis and improved management, the 5-year survival of breast cancer is over 80%.[49] With improved survival rates, increasing attention is now focused on the quality of life of these breast cancer survivors.[50] One concerning problem that affects breast cancer patients after surgery is the severity of pain, although the extent of the problem is unclear. The incidence of persistent pain after breast surgery has been reported to vary greatly, with some studies reporting rates as high as 50%.

A prospective study was done by Kulkarni et al.[51] to identify factors associated with acute postoperative pain after breast reconstruction . In this study, 2207 women were assessed preoperatively and postoperatively for pain experience, anxiety, depression and sociodemographic characteristics before surgery. The study was done over one week period using validated survey instruments. The results revealed younger age, bilateral reconstruction, severity of preoperative pain, anxiety, and depression were associated with more severe acute postoperative pain on all the pain measures.[51] A number of other studies have been carried out in recent times to look at the factors associated with the severity of acute postoperative pain after reconstructive surgery. A descriptive study done by Kroll et al.[52] reported that women undergoing free transvers rectus abdominis musculocutaneous flap reconstruction compared to those choosing deep inferior epigastric perforator flap reconstruction had higher doses of postoperative morphine requirement.[52] Gassman and colleagues on the other hand found no significant difference in pain between immediate and delayed postmastectomy reconstruction, when they retrospectively evaluated immediate postoperative pain and opioid use in 378 women.[53]

Postoperative pain management is still a common issue for women who have had breast cancer surgery. According to a recent survey, patients' top concern prior to surgery is pain.[54] Acute postoperative pain has a number of deleterious effects. It leads to an increased stress response

to surgery. This subsequently affects endocrine, metabolic, inflammatory, and immunological functioning, putting additional strain on multiple organ systems.[55] Also, poorly managed postoperative pain results in longer stay in the post anaesthesia care unit, longer hospital stay, lower patient satisfaction and quality of life and increased cost of healthcare services.[56–58] In 25–60% of patients, untreated acute pain can progress to chronic pain (paresthesia, phantom breast pain, and intercostobrachial neuralgia), resulting in a worse clinical outcome. One of the most important aspects of enhanced recovery after surgery is effective pain management. As a result, appropriate analgesic techniques must be chosen.[59]

2.3.2 Post mastectomy pain syndrome

Breast cancer surgeries cause significant acute pain and may progress to chronic pain states in 25% to 60% of patients.[6,50] The International Association for the Study of Pain (IASP) has established that pain can be considered chronic when it has persisted beyond the normal time of healing, with 3 months being considered 'the most convenient point of division between acute and chronic pain'.[60] The IASP taxonomy further proposes that when pain is associated with cancer, '3 months can be too long to wait before considering the pain as chronic'.[60]

Several studies have been carried out to identify factors associated with chronic pain after breast surgery.[61,62] The results thus far have been inconsistent, and the definition of patients who are susceptible to chronic post mastectomy pain remains uncertain.[61,63–65] Severe preoperative pain, severe acute postoperative pain, surgical factors such as the complexity of the surgery and the number of lymph nodes removed, neoadjuvant chemotherapy or radiotherapy, obesity, depression or anxiety, and age have all been indicated as risk factors.[66]

A retrospective cohort study conducted by Fecho et al.[67] in 196 female breast surgery patients revealed that nearly 60% of subjects experienced severe acute pain after surgery ($p<0.005$). [67] In this study, data were collected on: numerical rating scale (NRS) pain scores in the Post Anaesthesia Care Unit (PACU) and at 1 month and 6–12 months postoperatively; age; race; insurance; obesity; radiotherapy; chemotherapy; hypertension; anaesthesia care time; and intraoperative and PACU opioid use. The study also discovered that severe postoperative pain was experienced by 22.1% of subjects at 1 month and 8.2% of subjects at 6-12 months.[67] Earlier studies suggested that 13–43% of breast cancer patients experience surgery-related pain a year or more after mastectomy .[68] Perhaps, because participants who received concomitant axillary lymph node dissection, a known risk factor for persistent pain, were not included in the current

study, the estimated incidence of persistent postoperative pain is lower than earlier published rates.[67] Although the techniques of surgery has improved, the pain scores after surgery have not improved much.[69] Also noted was the fact that ,the complexity of the surgery was not a significant factor in determining postoperative pain scores at 1 or 6 -12 months. However, older age and systolic hypertension were found to be associated with less pain in the post anaesthesia care unit. There is literature evidence to support an association between high blood pressure and decreased pain sensitivity.[70,71] A recent prospective study showed that genetic polymorphism of the beta-adrenergic receptor is associated with both elevated blood pressure and a decreased risk for developing some chronic pain condition.[72] Several studies support the association between older patients and reduced postoperative pain. Race and body habitus played a role in postoperative pain scores. Non-Caucasians, clinical obesity, and high PACU opioid use were associated with greater postoperative pain at 1 month. Non-Caucasians, also had greater post- operative pain at 6–12 months.[67] This study was a retrospective study which is subject to several types of bias therefore must be interpreted with caution.

Spivey et al conducted a prospective observational study seeking to investigate the relative contribution of relevant surgical variables and to identify the relationship of baseline patient psychosocial characteristics to persistent postoperative pain at 6 months.[73] The study revealed that Pain Burden Index was variable between different types of breast surgeries and duration of the surgeries,however, there was no statistically significant difference between them at 6 months. The study however noted that axillary dissection was associated with a higher PBI than sentinel node biopsy and no axillary procedure($p<0.001$). Younger age ($p< 0.001$) and higher BMI ($p = 0.010$), as well as higher preoperative anxiety ($p = 0.017$), depression ($p < 0.001$), and catastrophizing scores ($p = 0.005$) correlated with higher 6-month PBI. Their findings corroborate what other researchers have discovered with regards to chronic pain after breast surgery.[73]

Pain after mastectomy has long been recognized as a serious post-surgical consequence. The features of this pain have been described long ago in literature. Most patients report it as a dull, burning, and aching sensation in the chest, axilla and ipsilateral upper extremities.[74] Constellation of these symptoms was referred to as post-mastectomy pain syndrome(PMPS) because it was thought to be a neuropathy, related to damage to the intercostobrachial nerve during surgical dissection.[75] The International Association for the Study of Pain (IASP) defines PMPS as persistent pain soon after mastectomy/lumpectomy affecting the anterior thorax, axilla, and/or medial upper arm persisting for more than three months after surgery.[76]

PMPS can develop immediately after surgery or it may occur months later and can persist for several years. The pain has a dermatomal distribution and it is neuropathic in nature. The pathophysiology is not completely understood but damage to the intercostobrachial nerve during breast surgery is believed to play a role.[77]

Post-mastectomy pain was once thought to be a rare complication of breast surgery, but it is now estimated that 20% to 50% of post-mastectomy patients unfortunately suffer from it.[78]The vast difference in estimates is partly due to definitional differences between research.[79] Studies that only include patients who arrive with neuropathic symptoms, the characteristic PMPS constellation, indicate a lower-than-average incidence.[80] Studies that include other sources of post-mastectomy pain such as lymphedema and musculoskeletal pain in addition to the PMPS symptoms record higher incidence.[81] Chronic pain can be exceedingly debilitating for women who have survived a mastectomy, lowering their quality of life and overall functioning abilities.[82,83]

A review of literature revealed paucity of data on the prevalence of PMPS in Ghana. There is the perception that the incidence of PMPS in the African population is low. Variawa et al.[84] carried out a descriptive cross-sectional studies in a tertiary referral hospital in South Africa to determine the prevalence of PMPS in adult female breast cancer patients following general anaesthesia without regional anaesthesia, as well as the impact of various clinical and demographic variables on the prevalence of PMPS. Ninety-two patients were assessed for chronic pain using the DN4 Questionnaire over a period of seven months. The prevalence of PMPS was found to be 38%. This incidence is similar to what other researchers have reported. From this data it can be inferred that a similar number of women in Ghana undergoing breast surgery for breast cancer are at risk of developing PMPS.

2.3.3 Postoperative nausea and vomiting

Post-operative nausea and vomiting is one of the most distressing complications associated with surgery. According to literature more than 22% of patients expressed that PONV gave them the highest level of concern during the perioperative period.[85] Although not associated with increased mortality, PONV is uncomfortable for patients, can prolong hospital stay, reduce patient satisfaction and increase the cost of healthcare.[86]

PONV is defined as nausea and or vomiting within the first 24 hours after surgery. Vomiting which is the actual oral expulsion of gastrointestinal contents as a result of contractions of the

gut and the thoracoabdominal wall musculature whilst nausea refers to a subjective feeling of the need to vomit.[87] The vomiting center lies in the medulla oblongata and comprises the reticular formation and the nucleus of the tractus solitarius. When activated, motor pathways descend from this center and trigger vomiting. These efferent pathways travel within the 5th, 7th, 9th, 10th, and 12th cranial nerves to the upper gastrointestinal tract, within vagal and sympathetic nerves to the lower tract, and within spinal nerves to the diaphragm and abdominal muscles.[88]

The vomiting center can be activated directly by irritants or indirectly following input from 4 principal areas: gastrointestinal tract, cerebral cortex and thalamus, vestibular region, and chemoreceptor trigger zone (CRTZ). The chemoreceptor trigger zone, is located within the dorsal surface of the medulla oblongata, on the floor of the fourth ventricle of the brain. It is in close proximity to the vomiting centre and unlike other brain centres it is not protected by the blood brain barrier. The CRTZ contains receptors that detect emetic agents in the blood and relays that information to the vomiting centre, which is responsible for inducing the vomiting reflex.[88,89]

Postoperative nausea and vomiting is common after administration of general anaesthesia with an overall incidence of 30%, while in high-risk patient groups the incidence may be as high as 70–80% despite newer antiemetic drugs.[90,91] A systematic review and meta-analysis done involving 23 studies and 22,683 participants from different countries between the years 2002 and 2018 showed that the overall prevalence of PONV was 27.7%.[92] The incidence of PONV at the study site has been reported by Amponsah[93] as 34% amongst patients 18 years and older undergoing general surgery, orthopaedic surgery, gynaecological surgery and Ear Nose and Throat surgeries. This was similar to research in Western Ethiopia where the incidence was 36.2 % in general population of 522 patients , from ages 5 years and upwards undergoing various elective surgery.[94] Another study done in Uganda at the Mulago Hospital among surgical patients aged 10 years and above ascertained the incidence of PONV to be 40.7%.[95] The incidence of PONV in non-Africans is significantly higher than in Africans. Non-African ethnicity is an independent risk factor for PONV.[86]

The aetiology of PONV is multifactorial. Apfel et al. proposed four main predictors of PONV: female gender, history of motion sickness and/or PONV, non-smoking, and receiving opioids. If none, one, two, three or four of these factors are present, the incidence of PONV is 10%, 23%, 39%, 61% and 79%, respectively.[91]

Anaesthetic technique is also considered an important risk factor for PONV. Choice of induction agents, maintenance of anesthesia and pain management perioperatively are all equally liable for inducing PONV. A volatile-free technique, utilizing propofol for anesthetic maintenance, has been demonstrated to reduce baseline risk by 19%.[96] The risk-reducing effects of total intravenous anesthesia (TIVA) has a similar risk reduction as the commonly used agents, ondansetron, dexamethasone and droperidol.[97]

Avoidance of general anesthesia with the use of regional blocks also significantly decreases the risk of PONV.[98] Klein et al.[99] reported significantly lower rates of PONV when comparing regional and general anaesthetic techniques.

Intraoperative and postoperative opioid use increases the risk of PONV in a dose-dependent manner.[93] Opioids such as fentanyl and morphine, commonly used to treat postoperative pain stimulate the D2 receptors in the CTZ. In addition, they reduce muscle tone and peristaltic activity, thereby delaying gastric emptying, inducing distension, and triggering the vomiting reflex.[100]

Different surgical procedures associated with high risk of PONV have been identified and the probable causes of PONV proposed. The most commonly cited procedures and their possible mechanisms are as follows: tympanoplasty (vestibular stimulation), ENT and oral surgery (swallowed blood), breast surgery (anxiety and emotional load), laparoscopy (peritoneal irritation), and abdominal and hysterectomy (GI and vagal stimulation). However no surgical procedure is an independent predictor of PONV. Some authors argue that these risk factors are more likely attributable to prolonged exposure to emetogenic anesthetics and underlying patient-related factors.[91]

Female gender in itself is a high risk for PONV, and those undergoing modified radical mastectomy with axillary lymph node dissection are at a relatively higher risk for developing PONV. Therefore, the need for an opioid free surgery cannot be overemphasised.[101]

In a randomized, double-blind, parallel-group, placebo-controlled study conducted by Yao et al.[102] with 72 patients coming for mastectomy, the intervention group received 25 ml of 0.5% ropivacaine and the control group had a sham block with physiological saline. The study revealed that preoperative SAP block with ropivacaine reduced the cumulative postoperative opioid consumption by 0.5% in the first postoperative 24 hours. Patients in the SAP block

group had a lower risk of developing postoperative nausea and vomiting compared to the control group. Comparable findings were observed in a single-center prospective study evaluating the effect of serratus anterior plane block on postoperative opioid consumption in patients undergoing mastectomy. Morphine consumption, VAS scores, and PONV, were significantly reduced postoperatively.[103]

2.4 Assessment of Pain severity

Pain is usually one of the major complaints of patients during the perioperative period, therefore accurate evaluation of pain is a fundamental requisite in the outcome assessment of patients coming for surgery. The characteristics that define pain and its impacts are pain intensity, pain-related impairment, pain duration, and pain affect. Different assessment instruments exist for each of these factors, which are explored in terms of benefits and drawbacks.[104]

In order to measure the degree of pain, a range of validated scales are utilized. Amongst these are the Visual Analogue Scale /Graphic Rating Scale(VAS/GRS), the Verbal Rating Scale (VRS), the Faces Pain Scale – Revised (FPS-R), and the Numerical Rating Scale (NRS) (NRS).[104,105]

2.4.1 Visual Analogue Scale/Graphic Rating Scale

The Visual Analogue Scale (VAS) consists of a straight line with the endpoints defining extreme limits such as ‘no pain at all’ and ‘pain as bad as it could be’ (Fig. 2.12).[106] The patient is asked to mark his pain level on the line between the two endpoints after explaining the end points to the patient. The distance between ‘no pain at all’ and the mark then defines the patient’s pain. A line-length of 100mm or 150 mm showed the smallest measurement error compared to 50mm and 20mm versions and seems to be most convenient for respondents.[107]

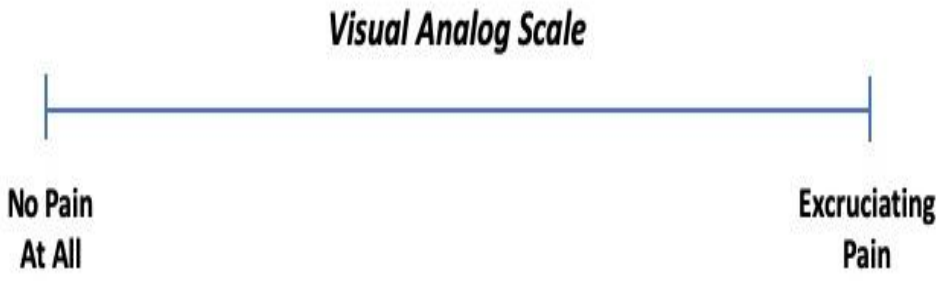

Figure 2.12: Visual Analogue Scale

(Source:greatbrook.com)

The VAS can be modified into a Graphic Rating Scale(GRS)by adding the descriptive terms 'mild', 'moderate', 'severe' and "unbearable agony".[104] Respondents are required to select one of five phrases that best depicts the severity of their suffering. To make administration easier, the five words are assigned values: 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain, and 4 = unbearable pain. The use of words or adjectives to describe the severity of pain makes quantitative comparisons between patients challenging. In several studies, VAS and GRS have been demonstrated to be sensitive to treatment effects.[107–109] They were found to correlate positively with other self-reporting measures of pain intensity.[110]

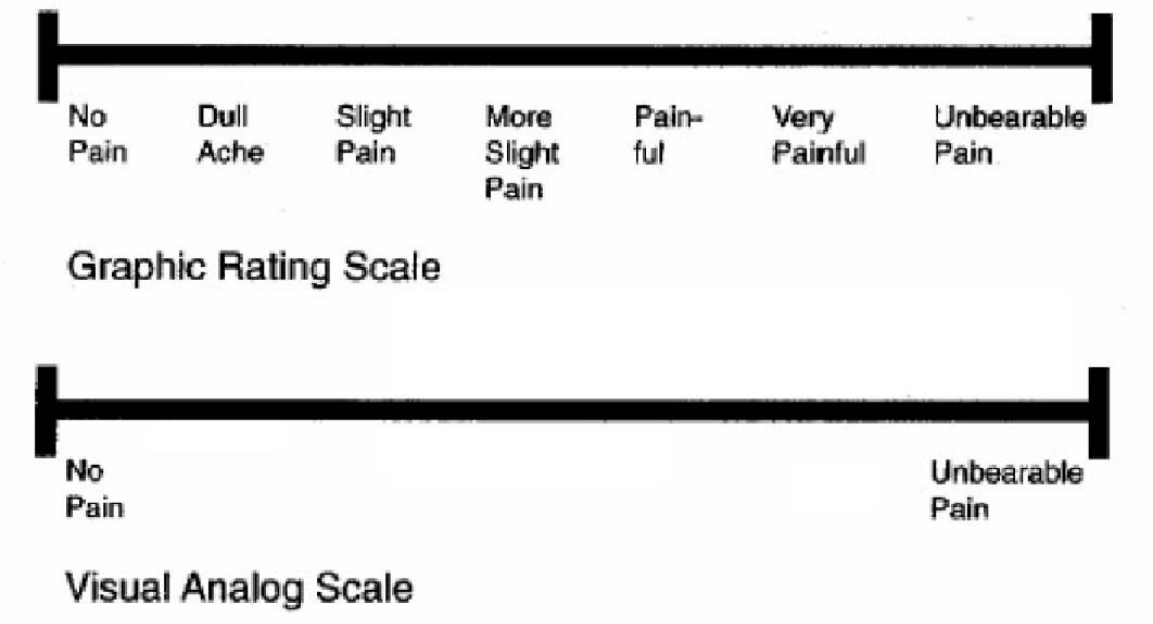

Figure 2.13: Graphic Rating Scale above and Visual Analog Scale below

(Source:semanticscolar.org)

2.4.2 Numerical Rating Scale (NRS)

The NRS typically consists of a series of numbers with verbal anchors representing the entire possible range of pain intensity.[104] Generally, patients rate their pain from 0 to 10, from 0 to 20, or from 0 to 100 (Fig 2.14). In multiple investigations, the NRS has been shown to be equally sensitive as the VAS, independent of the scale used (a 0 – 10 scale or a 0 – 100 scale).[40,110]In contrast to the VAS/GRS, only the numbers themselves are valuable answers, meaning that there are only 11 possible answers in a 0–10, 21 in a 0–20 and 101 in a 0–100 point NRS. It thus allows only a less-subtle distinction of pain levels compared to VAS/GRS, where there are theoretically unlimited number of possible answers. Numerical Rating Scales have shown high correlations with other pain-assessment tools in several studies.[108,110] The feasibility of its use and good compliance have also been proven.[111,112] It is often used in telephone interviews because it can be administered easily.[110] The downside of the NRS is that, results cannot necessarily be treated as ratio data as in VAS/GRS.[113]

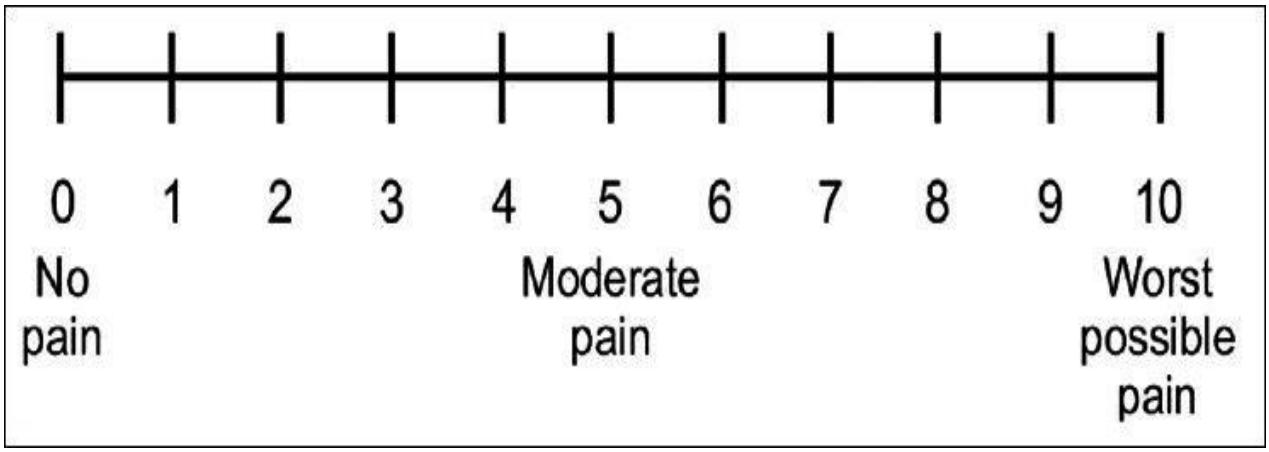

Figure 2.14: Numerical Rating Scale

(source:researchgate.net)

A research conducted by Bijur et al.[114] to validate the use of the NRS in the emergency department showed that the NRS has a strong linear correlation with VAS ratings at all time periods during the research period (r = 0.94, 95 percent confidence interval (CI) = 0.93 – 0.955t. 57]. This research involved 108 individuals who presented to the emergency room with acute pain. They were instructed to assess their discomfort by marking a horizontally positioned 10cm VAS with anchor points indicating "no pain" and "worst possible pain." They were also asked to rate their pain on a scale of 0 to 10 on the NRS, with 0 representing "no pain" and 10

representing "worst possible agony." The sequence of the scales was changed at random, and the measures were repeated 30 and 60 minutes after the baseline.

The NRS had a minimum clinically meaningful difference of 1.3 (95 percent CI 1.0 – 1.5) while the VAS had a difference of 1.4 (95 percent CI 1.0 – 1.5). Because the majority of patients in their research experienced moderate to severe pain, their findings must be taken in this context and should only be applied to patient groups experiencing considerable acute pain. Furthermore, the degree of agreement between the NRS and the VAS in this study may have been overstated since the patient's answer to the second pain scale delivered is not independent of their response to the first scale administered.

2.4.3 Verbal Rating Scale

In a Verbal Rating Scale (VRS) adjectives are used to describe different levels of pain.[104] The respondent is asked to select the adjective that best describes the severity of the pain. Two endpoints should be defined, similar to the VAS, such as "no pain at all" and "extremely intense pain." Distinct descriptors that indicate different pain-intensity levels are placed in order of pain severity between these extremes. In most clinical trials, four- to six-point VRS are used. The behavioural rating scale is a type of VRS in which different pain levels are expressed by phrases that include behavioural parameters.[115] VRS, like VAS, has been demonstrated to have a good correlation with other pain-measurement techniques.[108,116] Even though subjects must read the complete list before answering, which takes time respondent compliance is often as good or even better than that of other instruments.[110,111]

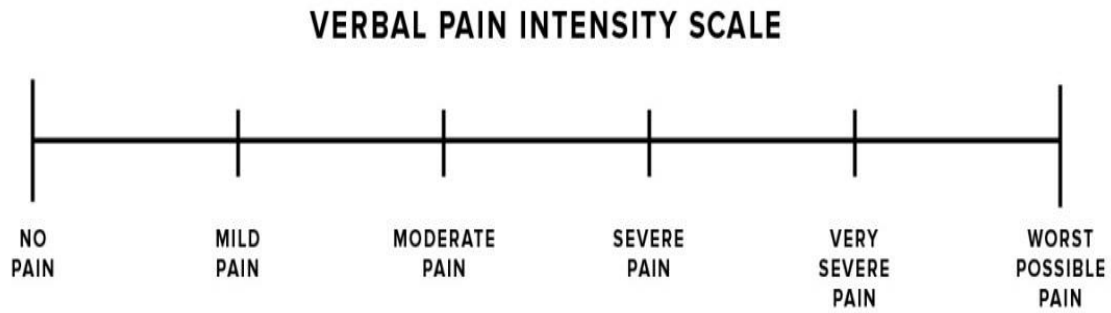

Figure 2.15: Verbal Rating Scale

(Source:healthline.com)

2.4.4 The Colour Analog Scale (CAS)

The Colour analog scale (CAS) is yet another pain scale that has been validated for use in children aged 5years and older but its reliability has not been established. It is a 10cm scale with colour gradations, with "no pain" at the bottom and "most pain" at the top. (Figure 2.12) The CAS resembles a ruler, with one side showing a wedge-shaped figure filled with colour that gradually progresses from white to red as the figure widens and the other side showing corresponding numerical ratings from 1 to 10 cm, divided into 0.25-cm increments.[117]

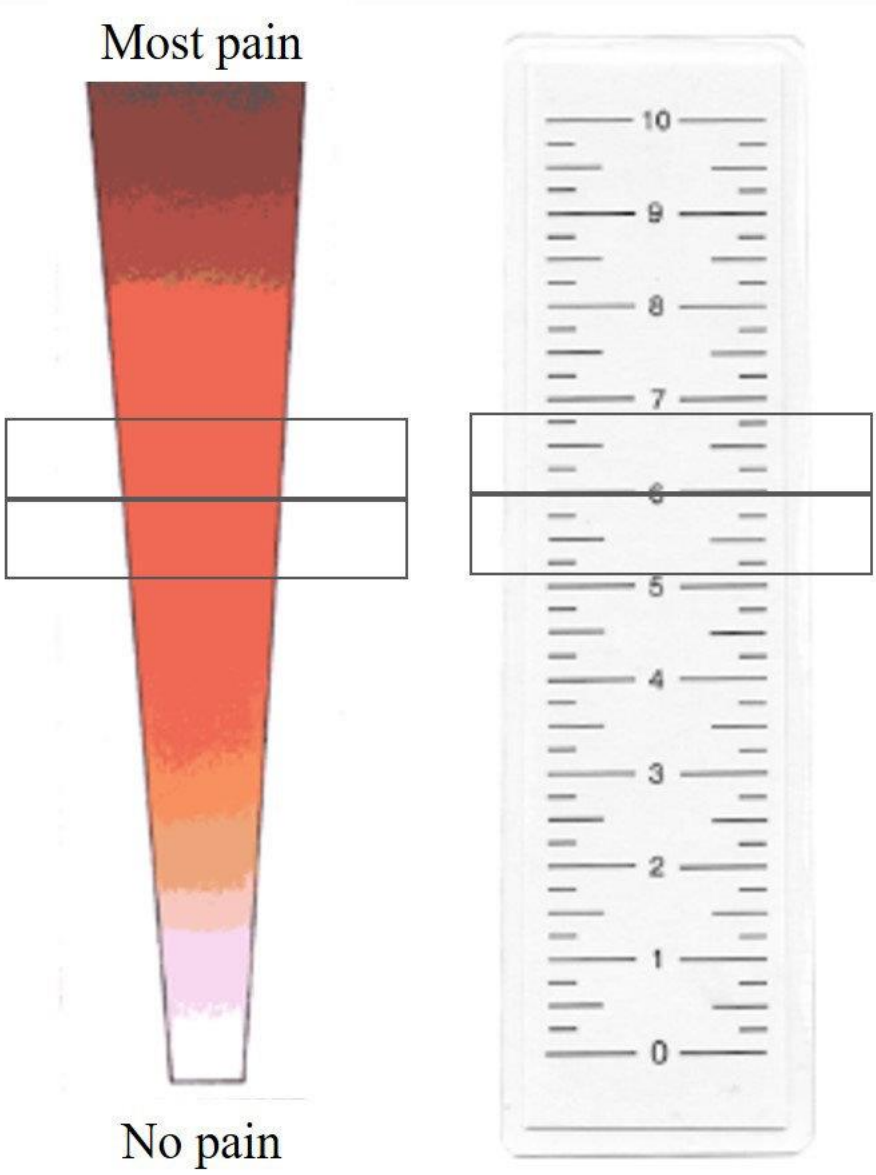

Figure 2.16: Colour Analog scale

(source:researchgate.com)

2.4.5 Faces Pain Scale-Revised

FPS-R (Figure 2.17) is a self-report pain intensity scale derived from the Faces Pain Scale developed for use in children.[118] It is especially advised for usage in very young children. Unlike the numeric scales, the faces scales do not require the concept of magnitude or seriation and can therefore be used by preschool-aged children. [117]It shows good correlation with visual analog pain scales in children between the ages of 4-16 years. It is very easy to administer and it only requires photocopied faces. The added benefit is the absence of smiles and tears in this scale. It consists of six faces that depict the patient's level of pain/hurt, and the patient is asked to select the face that best reflects their level of pain/hurt. The chosen face is scored 0, 2, 4, 6, 8, or 10 from left to right, with "0" equaling "no pain" and "10" equaling "very painful." The person administering the scale is advised not to use words like "happy" or "sad" to describe the faces on the scale because the scale is intended to measure how children feel on the inside rather than how their faces look.[110] When it comes to responsiveness, the scale has been proven to be less sensitive than the VAS, VRS, and NRS, with the NRS being the most sensitive of the four scales.[119] Although it was initially designed for children, it has also been validated for use in adults and individuals with cognitive disability.[119] Because the NRS or VRS is easier and simpler to administer, both patients and physicians prefer it over the VAS.[53]

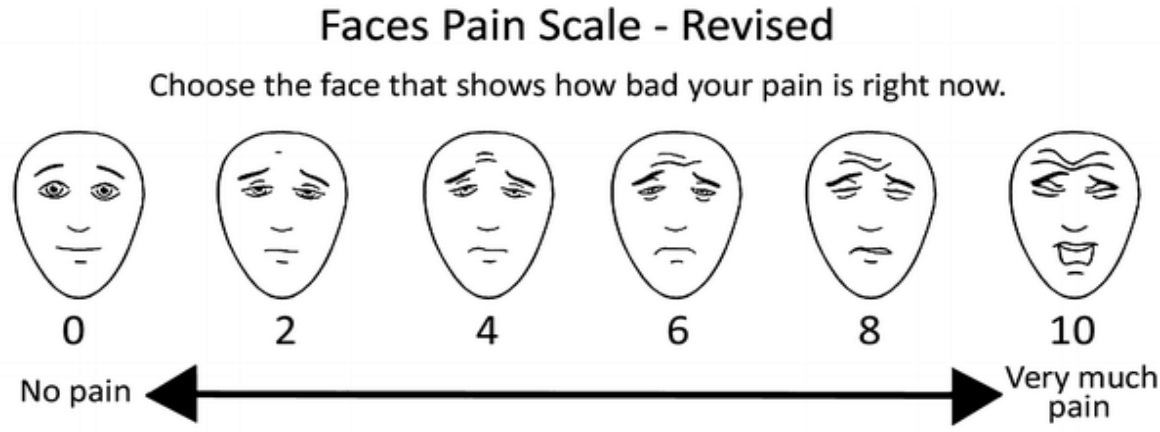

Figure 2.17: Faces Pain Scale-Revised

(Source:researchgate.com)

A literature review of studies specifically comparing the NRS, VRS, and/or VAS for unidimensional self-report of pain intensity showed that the NRS has better responsiveness and

it is simple to use.[120] More so, it is applicable in most situations therefore it is recommended as the tool of choice in most investigations. However, the VAS is the most often used pain scale clinically. In recent times more investigators are leaning towards the use of NRS because research conducted on patients with joint pain (hip and knee) using Rasch analysis to investigate the responsiveness of the pain VAS revealed that the pain VAS is a valid tool for measuring pain at one point in time. However, the pain VAS does not behave linearly, therefore standardised response means vary along the trait of pain.[121]

2.5 Pain management in breast surgery

One of the factors for the occurrence of persistent breast cancer pain syndrome and phantom breast is the suboptimal management of perioperative pain.[15,122] Traditionally, opioids have been the main source of pain relief during breast surgery. Along with being effective and reliable, opioids are readily available and easily titrated, explaining their relative preponderance in the perioperative period.[123] Opioids however are not devoid of side effects. Commonly encountered side effects are pruritus, postoperative nausea and vomiting, respiratory depression, constipation, ileus, urinary retention, general fatigue, headache and drowsiness.[124,125]The relationship between opioid dose and complications in the acute postoperative period is poorly studied and adverse effects that range from extremely severe to mildly inconvenient seem to be additive with increasing doses of opioids.[126] The analgesic effect of opioids is dose dependent, but severe respiratory complications may occur even with small doses.[123]

Increasing opioid usage in the postsurgical patient is also associated with increased risk of opioid associated hyperalgesia leading to chronic pain.[127] Serious side effect associated with opioid use is death as illustrated by nearly 15000 prescription opioid related overdose deaths in 2008 significantly higher than the annual deaths attributable to heroin and cocaine combined.[128]

Opioids and volatile anaesthetics have been associated with immunosuppression and thus the risk of tumour recurrence.[129–131] Opioids promote tumour growth and metastasis by modulation of cellular and humoral responses leading to immunosuppression, direct action on tumour cells and immune or endothelial cells and the activation of neuroendocrine-mediated stress response leading to the progression of metastasis and angiogenesis. However, there are conflicting data

with regard to evidence of implication of opioids with increased risk and number of metastases .[132,133]

The recent opioid epidemic, due in part to persistent use of perioperative opioids, raises questions about the systematic administration of opioids during anaesthesia and the development of new non-opioid strategies.[134] One approach for pain management include the use of regional anaesthesia which provides effective anaesthesia and analgesia in the perioperative setting. Although the beneficial analgesic effect of regional block is well known, data are emerging for the other potentially beneficial effects of regional anaesthesia and analgesia on other perioperative outcomes.[135]These benefits include, decreased postoperative nausea and vomiting(PONV), fewer post-operative pulmonary complications and decreased duration of post-anaesthesia care unit stay.[136]There is laboratory and animal evidence for the importance of good analgesia, with sparing of opioids, in preventing cancer recurrence.[135]

Regional anaesthesia may reduce cancer progression by attenuation of the surgical stress response, better analgesia , and reduced opioid usage, and by direct protective action of local anaesthetics on cancer cells migration.[132]There has been some evidence to suggest regional anaesthesia reduce the incidence of postsurgical chronic pain in patients undergoing mastectomy.[137] Katipamula et al[43] demonstrated that by providing adequate analgesia by regional anaesthesia during breast surgery, chronic breast pain syndromes appear to be ameliorated. This finding is supported by a meta-analysis and Cochrane review for persistent pain after breast surgeries which revealed that pre-operative regional blocks are effective for reducing chronic pain after breast cancer surgery.[139]

These findings have heightened interest in regional anaesthesia for breast surgery, including techniques such as local infiltration, thoracic paravertebral, thoracic epidural and peripheral nerve blocks.[11,140,141] The widespread adoption of these techniques is hampered by concerns regarding their technical complexity and the risk of serious complications such as hypotension, pneumothorax, central neuraxial block and opposite side spread of injectate.[13] More recently, ultrasound-guided interfascial plane blocks such as pectoral(PEC) nerve blocks types1 and 2 and the serratus plane block have gained popularity.[12,13,142]

2.5.1 Serratus anterior plane block

Regional anaesthesia such as serratus anterior plane block is an ideal alternative to other regional anaesthetic techniques in the management of intraoperative pain during breast

surgery.[13] It has become popular due to its efficacy, relative ease, and limited side-effect profile.[143]The serratus anterior muscle originates from the anterior aspect of the 1st to 8th ribs and inserts on the medial border of the scapula. It consists of 7-10 serrated tendinous projections that originate on each rib and is innervated by the long thoracic nerve.[144] The serratus anterior is bounded by deep and superficial potential spaces. At the level of the fifth rib, the superficial plane is formed from the anterior aspect of the serratus anterior and the posterior aspect of the latissimus dorsi muscle. The deep plane is formed from the posterior aspect of the serratus anterior and the external intercostal muscles and ribs.[13]Either plane will achieve analgesia to the anterolateral chest wall with reportedly similar efficacy and an equivalent area of cutaneous sensory loss.[12,145,146]

The SAP block targets the lateral cutaneous branches of the thoracic intercostal nerves, which arise from the anterior rami of the thoracic spinal nerves and run in a neurovascular bundle immediately inferior to each rib. At the midaxillary line, the lateral cutaneous branches of the thoracic intercostal nerve traverse through the internal intercostal, external intercostal, and serratus anterior muscles, innervating the musculature of the lateral thorax.[147] These branches of the intercostal nerves, therefore, travel through the two potential spaces described above. Local anaesthetics injected into these planes will spread throughout the lateral chest wall[146,147] resulting in anaesthesia of the T2 through T9 dermatomes of the anterolateral thorax.[13]

The SAP block has been used effectively for management of pain in the context of rib fractures[148] rib contusions, thoracoscopic surgery [143] thoracotomy[149],breast surgery[12],and post-mastectomy pain syndrome.[145,150] Two case reports written by Khemka et al[151] demonstrated that the SAP block cause chest wall analgesia lasting 12 hours following breast surgery. Although their report showed good results they encouraged other anaesthesiologists to formally investigate and validate the efficacy of SAP block for breast surgery.[149,151] Rahimzadeh[8] and colleagues in Iran in their randomised prospective study established that patients who had ultrasound guided SAP block had significantly lower pain scores and opioid consumption compared to control groups who did not get a block .Their study was limited by the lack of a control group that received placebo injections and a small sample size. Bhoi et al.[152] reported a case of a morbidly obese patient (BMI 43.7 kg/m2) considered a candidate for breast surgery, the serratus anterior plane block with ropivacaine together with propofol sedation was effective to provide analgesia during the operation. Patient did not require rescue analgesia until she was discharged home the next day on NSAIDS. Although Blanco et al[13] concluded that superficial

plane block is more effective in SAP block, in this particular case, the authors used a deeper plane block and were very satisfied with the results obtained.

Similarly, in a recent prospective randomised controlled trial by Elsabeeny et al.[153] to evaluate the efficacy of ultrasound-guided SAPB and ESPB versus IV morphine analgesia in perioperative pain control of breast cancer patients undergoing modified radical mastectomy, they reported that both SAPB and ESPB can be used as an efficient alternative to IV opioid analgesia with better analgesic profile, less postoperative opioid consumption, prolonged time to receive first dose analgesia and fewer side effects. However, they documented a longer procedural time for ESBP than for SAPB. They explained that ESBP takes a longer time because the plane at which injectates are deposited are in deeper planes. However, both blocks can be considered simple and when performed under ultrasound guidance can be relatively safe.

In contrast to what most trials have reported, a recent RCT showed that SAPB did not improve analgesic outcomes in patients who had ambulatory breast cancer surgery. The investigators in this study argued that breast surgery is a broad term which involves different types of surgeries with different degrees of pain, therefore their block may not have provided the same level of analgesia for the different types of surgeries hence the outcome of their study.[154]

Some studies have been carried out to assess the analgesic efficacy of Serratus anterior plane block for thoracic surgery. It is reported that SAP block has similar analgesic profile to thoracic epidural with less haemodynamic instability.[155] In a systematic review and metanalyses of 7 RCT with 489 patients in order to assess the analgesic efficacy of SAP block for peri-operative pain control in video assisted thoracoscopy surgery(VATS) revealed that SAPB reduced pain scores peri-operatively, compared with controls($P < 0.001$).SAP block also reduced the use of postoperative opioids ($P < 0.03$) and decreased the incidence of nausea and vomiting($P < 0.002$).[156]

The serratus anterior block can be performed either superficial or deep to the serratus anterior muscle.[145] There is a debate on which technique is superior.

Superficial serratus anterior plane block.

This approach involves injecting the local anaesthetic in the fascial plane between the latissimus dorsi and the serratus anterior muscle at the level of midaxillary line. Proponents of

the "original" superficial serratus block argue that the block gives successful analgesia without the potential hazard of advancing the needle towards the pleura.[157,158] Breast oncologic surgeons performing axillary interventions (SLNB or ALND) on patients who received superficial serratus block have observed local anaesthetic fluid infiltration and disruption of the axillary tissue planes, particularly around the level I lymph nodes, which are the primary surgical target for patients undergoing axillary biopsy or dissection.[159] Local anaesthetic spread following superficial serratus block also blocks the long thoracic and thoracodorsal nerves, interfering with oncologic surgeons' intraoperative stimulation of these nerves proximally thereby making efforts to identify and preserve them difficult.[160]

Deep serratus anterior plane block

This technique involves injecting the local anaesthetic in the fascial plane between the posterior surface of the serratus anterior muscle and the external intercostal muscle at the level of the midaxillary line.[158] Although there is a potential increased chance of pneumothorax with this technique especially when the needle is placed between the serratus anterior muscle and the external intercostal muscle, this risk can be significantly reduced by injecting on the surface of the rib.[161] Using rib as a landmark has enabled some clinicians to administer this block even without ultrasound guidance. Thoughtful consideration of anatomy arguably favours the deep serratus block, as injection in the fascial plane below the serratus muscle theoretically facilitates blockade of higher-order lateral cutaneous intercostal nerves, which are known for their extensive ramification and collateral branching.[162]

Initial study conducted by Blanco et al[13] used the superficial technique and the results were very satisfactory. Bhoi [163] and colleagues set out to investigate which of the two techniques was superior. They used 20 patients coming for breast surgeries. Twelve patients received a deep block and 8 patients received a superficial block. Postoperative fentanyl consumption was higher in the deep block group compared to the superficial block group. Their study demonstrated a better pain control in the superficial block group which corroborated the initial work by Blanco et al. However, they were very careful in extrapolating their findings to the larger population because of their small sample size. Interestingly, Piracha et al[145] in their case reports of 4 patients with post mastectomy pain syndrome, found a deep serratus anterior plane block superior to the superficial blocks, in the management of these patients. A study conducted by Edwards et al investigating the difference in opioid consumption and postoperative analgesia between superficial and deep and SAPB for patients undergoing mastectomy

revealed that subjects who received deep SAPB required 30% less oral morphine equivalents and reported lower pain scores.[164]

A retrospective study conducted by Hards[165] and colleagues in the UK, over a period of six months compared postoperative pain scores of patients who had had mastectomy. One group had received serratus anterior plane block using a combination of 0.375% levobupivacaine, 1: 200 000 adrenaline and 1mcg/kg clonidine which were injected under direct observation by the surgeon. The second group received only wound infiltration with local anaesthetic without any block. Their study revealed a better pain control with the SAP block group compared to those who received local infiltration only. Their study was limited by its retrospective nature and a single centre design. More so, huge volumes of local anaesthetics(approximately 50ml) were used in the SAP block compared to what has been used in similar studies.[8]

A propensity-matched retrospective cohort study conducted by Abdallah et al.[166] at the Women's College Hospital, University of Toronto which reviewed the medical records of 225 patients who had undergone mastectomy with either PEC 1 block, SAP block or no block revealed that Pectoralis and serratus blocks were each associated with a reduction in postoperative in-hospital opioid consumption and PONV compared with conventional opioid-based analgesia after ambulatory breast cancer surgery. More importantly, the study revealed that SAP is not inferior to PEC 1 block. Although this study had a huge sample size, it is limited by the fact that it is a retrospective study and there may be potential errors in data collection and documentation. More so, being an observational study, conclusion on potential association can be made but not causal relationships.

The results from these studies offer evidence that SAP block provides good postoperative analgesia and reduce prolonged hospital stay which can significantly reduce the cost of healthcare delivery. However, more studies need to be conducted to validate this claim since the block has been utilised for a relatively short time.

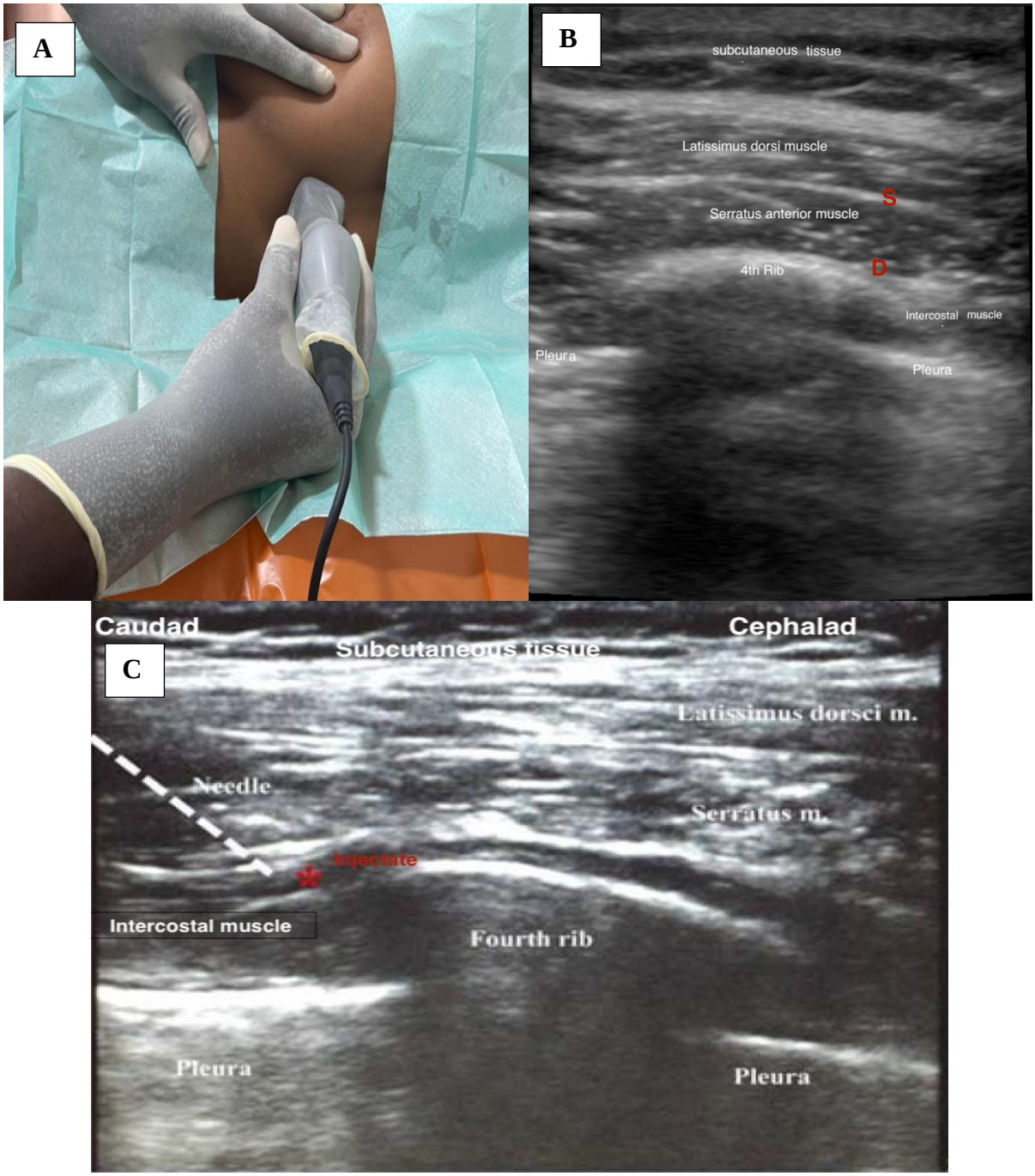

Figure 2.18: Steps in performing SAP Block. (S=superficial serratus anterior fascial plane; D= deep serratus anterior fascial plane)

2.6 Local Anaesthetic Agents

Local anaesthetic agents suppress action potentials in excitable tissues by blocking voltage gated sodium channels.[167] In doing so, they inhibit action potentials in nociceptive fibres and so block the transmission of pain impulses.[168] The molecular structure of local anaesthetics

contains a lipophilic aromatic ring system attached by an ester or amide intermediate chain to a hydrophilic tertiary amine.[169] Variation of the amine or aromatic ends changes the chemical activity of the drug. All currently available clinically useful local anaesthetics exist as either aminoamides or aminoesters.[170] Aminoesters are hydrolyzed by plasma cholinesterases and aminoamides are degraded by hepatic carboxylesterases.[171] Commonly used amino amides include lidocaine, mepivacaine, prilocaine, bupivacaine, etidocaine, ropivacaine and levobupivacaine.[172] Commonly used amino esters include cocaine, procaine, tetracaine, chloroprocaine and benzocaine.[173]

Bupivacaine is a chiral compound, used clinically for 50 years.[174] It is a long acting amide. It is a racemic mixture of R and S enantiomers with profound cardiotoxicity in higher doses.[175] The S enantiomer, Levobupivacaine has reduced intensity and duration of motor block but less cardiotoxic.[175] Bupivacaine is prepared as a 0.25% and 0.5% (with or without 1:200 000 adrenaline) solution. A 0.5% preparation containing 80 mg/ml glucose with a specific gravity of 1.026 is available for subarachnoid block. The maximum safe dose is 2mg/kg.[176]

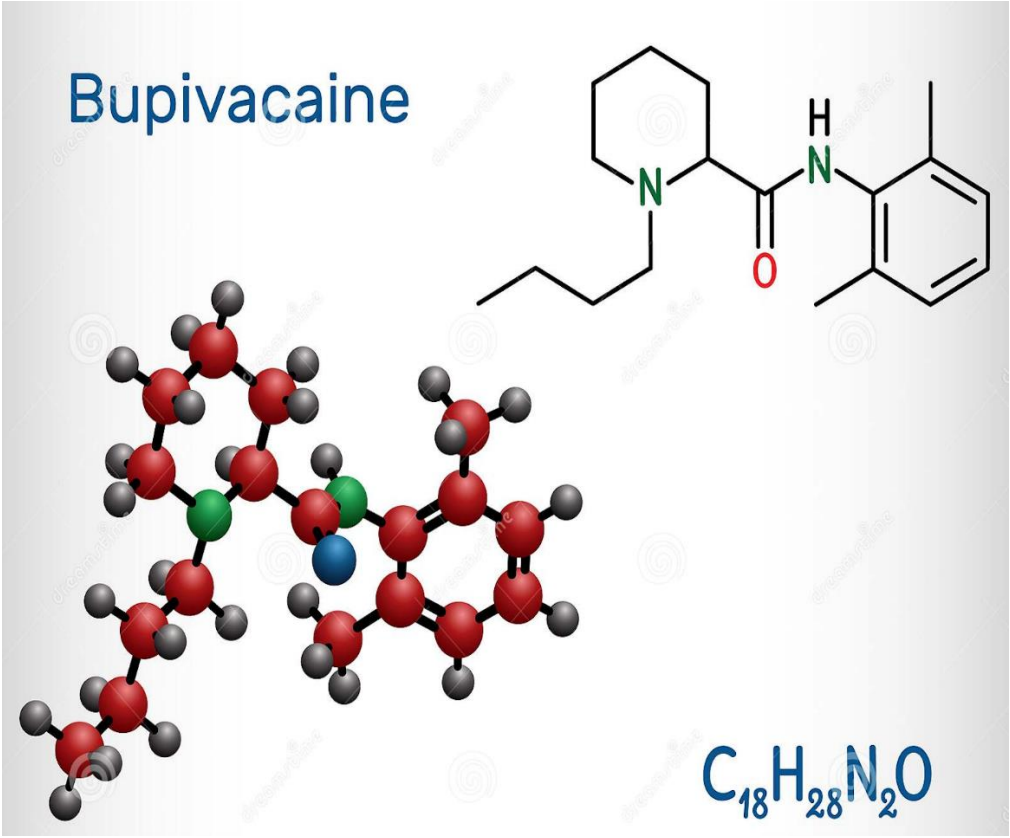

Figure 2.19: The chemical structure and formula of bupivacaine

(Source: dreamstime.com)

2.6.1 Local Anaesthetic Systemic Toxicity

Local anaesthetics cause both systemic and local toxicity. Systemic toxicity relates to the relatively narrow difference between therapeutic plasma levels and toxic levels.[167] The absorption of local anaesthetic varies widely depending on the site of administration and presence of vasoconstrictors.[176] Raised systemic blood levels of local anaesthetic lead initially to the central nervous system(CNS) and then to cardiovascular toxicity.[177] They penetrate the brain rapidly and have a biphasic effect. Inhibitory interneurons are initially blocked causing excitatory phenomenon such as circumoral tingling, visual disturbance, tremors and dizziness. This is followed by seizures and finally coma and apnoea.[176]

In general, systemic cardiovascular toxicity is seen at a plasma concentration far greater than that for CNS toxicity.[171] However, although all local anaesthetics can cause hypotension, arrhythmias, and myocardial depression, more potent agents like bupivacaine are predisposed to devastating outcomes, such as fatal cardiovascular collapse and complete heart block.[171]

2.7 Butterfly iQ

The Butterfly iQ(iQ Butterfly Network, Inc, Guilford, CT, USA) is a new point-of-care ultrasound (POCUS) device that was introduced in 2018. It is powered by an ultrasound on chip technology instead of piezoelectric crystal. It has a matrix of 9000 micro-machined sensors that can be handled electronically and made to behave like a convex, linear and sectorial probes.[178,179]

The butterfly iQ works using a mobile phone or tablet with an iOS or android app. The app is intuitive, simple and responsive. It combines flexibility and mobility in a single probe with preset modes replacing the need for multiple transducers.[178] It has 20 imaging pre-sets that can be used in abdominal, cardiac, lung, bladder, nerve, vascular, musculoskeletal, ocular and obstetric point-of-care imaging.[180]

The cost of the device (approximately $2000, plus a required $420 annual subscription fee to the cloud-based image storage) places it within reach of some individual clinicians, and many healthcare institutions, even in resource limited settings. The battery life is reasonably adequate, usually enough to last an entire 12-h shift on a full charge when being used intermittently.[178]

It has several advantages over cart-based machines. It is cheaper and has good use in areas with limited floor space and unreliable power. Integration with the user's mobile phone or tablet, and use of silicon-chip based technology obviates the need for multiple transducers.[180]

Some of the limitations of the Butterfly iQ is lower resolution in the echocardiography mode compared to other modes.[180] Also, similar to other pocket-sized devices, the Butterfly iQ lacks spectral Doppler. Another potential challenge with the Butterfly iQ is the fact that internet connection is required to upload and store the images in the cloud.[180] Without reliable internet access the images remain in the "outbox" where they can easily be deleted. The device also periodically overheats rendering further scanning impossible until the device cools.[178]

2.8 Patient Satisfaction

Although it is identified as an important quality outcome indicator to measure the success of the services delivery system, patient satisfaction is not a well-defined concept. In the literature, there is no agreement on how to define the idea of patient satisfaction in healthcare.[181]

Many authors have differing opinions on what constitutes patient satisfaction. Patient satisfaction appears to express attitudes toward care or parts of care, according to Jenkinson et al.[182] Patient satisfaction was defined by Mohan et al.[183] as patients' emotions, feelings, and perceptions of delivered healthcare services. Patient satisfaction is characterized as a patient-reported outcome measure in Donabedian's quality assessment modeL.[181] Patient evaluation of care is critical for identifying areas for improvement, such as strategic structuring of health programs that often exceed patient's expectations and benchmarking.[181]

In general, there are two ways to assess patient satisfaction: qualitative and quantitative. Patient satisfaction can be accurately measured using the quantitative technique. The most popular assessment instrument for conducting patient satisfaction studies has been standardized questionnaires (either self-reported, interviewer-administered, or over the phone).[184]

In this study a simple qualitative assessment was used by asking patient to rate their satisfaction with their postoperative pain management. Patients were asked to rate their satisfaction rate as very satisfied, somewhat satisfied, neutral, somewhat dissatisfied and very dissatisfied.

CHAPTER 3: MATERIALS AND METHODS

3.1 Study Design

The study was a prospective randomized double-blind placebo-controlled trial. A data abstraction form (Appendix 1) was used to collect relevant data for the study.

3.2 Study Site

The study was conducted over a 12-month period at the surgical block of the Korle Bu Teaching Hospital, a major tertiary and largest referral centre in Ghana. The hospital has approximately 1800 bed capacity and 23 theatres. Seven of these theatres are located on the first floor of the surgical department. There are 4 general surgical teams at the hospital with each having an elective list on a separate but fixed day in the working week. The four teams have their sub-specialization or areas of interest. Breast surgeries are mainly but not solely done by Unit 2 on Thursdays. The first-floor surgical suite has a 7-bed recovery ward/PACU which sometimes doubles as a high dependency unit.

3.3 Study Population

The study population was made up of all American Society of Anaesthesiologists (ASA) classes I and II, aged 18 to 70 years who were scheduled to have breast surgery at the Surgical Department during the study period.

In order to minimise confounders from surgical technique in this study, participants were recruited from the surgical list of only Surgical Unit 2. There were two consultants and two senior residents performing all the surgeries in this team.

3.4 Inclusion Criteria/Exclusion Criteria

3.4.1 Inclusion criteria

All patients with an American Society of Anaesthesiologists(ASA) physical status I and II aged 18 to 70 years coming for elective breast surgery who gave written informed consent were recruited for the study.

3.4.2 Exclusion criteria

Patients with the following characteristics were excluded from the study:

- Known allergy to bupivacaine
- Bleeding disorders
- Infection in the posterior and mid axillary region
- Pregnant patients
- Weight less than 50kg or obesity (BMI >35kg/m2)

3.5 Sampling and Sample Size Determination

A study conducted by Rahimzadeh[8] and colleagues on impact of ultrasound guided serratus anterior plane block on post mastectomy pain revealed that the intervention group(SAP block with bupivacaine) had significantly lower VAS scores at 1, 6, 12 and 24 hours postoperatively compared to the control group that received no block. At 6 hours postoperatively, the mean VAS (μ_1) was 2.3 with a standard deviation (σ_1) of 0.3in the intervention group and 2.6 (μ_2) with a standard deviation (σ_2) of 0.6 in the control group. The greatest difference in mean VAS scores between the two groups was at 6 hours. Therefore, the mean VAS score at 6 hours will be used to calculate the sample size in our study. Based on a power of 90% and a confidence level of 95%, the sample size for each group was calculated using the formula:

$$N = \frac{(u+v)^2(\sigma_1^2 + \sigma_2^2)^2}{(\mu_1 - \mu_2)^2}$$

where N = the sample size in each of the groups

σ_1 = standard deviation of VAS at rest at 6 hours postoperatively in the intervention group

σ_2 = standard deviation of VAS at rest at 6 hours postoperatively in the control group

μ_1 = mean VAS at rest at 6 hours postoperatively in the intervention group

μ_2 = mean VAS at rest at 6 hours postoperatively in the control group

u = standard normal deviate for significance level ($\alpha = 0.05$)

v = standard normal deviate for power of 90% ($\beta = 0.10$)

If u = 1.96 and v = 1.28 then,

The sample size is estimated as 23 participants per each group. To allow for losses to follow-up, incomplete data and other contingencies, 10% of the calculated sample size was added, increasing the total sample size to approximately 50 participants.

3.6 Procedure Used

3.6.1 Selection into study

Selection into the study was by consecutive inclusion of all patients who met the inclusion criteria and gave informed consent until the sample size was achieved.

3.6.2 Randomization into groups

Patients were randomized into two groups the day before surgery during the preoperative visit. The intervention (bupivacaine) group and the control (saline) group. Placement into the groups was by simple randomization using balloting without replacement. Twenty-six ballots were labelled 'X' and another 26 ballots labelled 'Y' to represent the two arms of the study. Each ballot was folded in two and then folded again three times. The ballots were then placed in an opaque envelope. After a patient who met the criteria had been selected into the study, the principal investigator drew a ballot from the opaque envelope to determine which group (either 'X' or 'Y') the patient would be randomized to. The ballot which was picked by the principal investigator was then discarded. The process was repeated for subsequent patients who were selected into the study until all the ballots in the opaque envelope had been picked.

3.6.3 Blinding

This was a double-blinded study. The principal investigator and the patient were both blinded to the interventions. The code determining the identity of the 2 groups (i.e., which group was the bupivacaine group and which was the saline group) was known only to one of the supervisors who revealed the code after all the data had been collected and analysed.

3.6.4 Description of procedure

All patients who were recruited into the study were assessed preoperatively. During the preoperative assessment, the NRS was thoroughly explained to the study participants. The supervisor who had the code to the identity of the groups prepared two sets of syringes with

the label ‘X’ or ‘Y’ depending on the group a patient had been randomized to and handed it to the principal investigator. The syringes contained either 0.25% plain bupivacaine or 0.9% normal saline. Both solutions were clear and colourless, therefore it was impossible for the principal investigator administering them to tell the two apart. All the patients were given standardized general anaesthesia before the block was performed.

After establishing Association of Anaesthetists of Great Britain and Ireland (AAGBI) standard monitoring with a non-invasive blood pressure (NIBP) cuff, 3 lead Electrocardiogram (ECG), and a pulse oximeter, baseline parameters, heart rate (HR), NIBP, and oxygen saturation (SpO_2) were noted. After preoxygenation for 3 minutes, anaesthesia was induced with 1-2mcg/kg of IV Fentanyl and 2-3mg/kg of IV Propofol. Airway was secured with a laryngeal mask airway. Anaesthesia was maintained with Isoflurane/Oxygen/Air mixture to maintain a minimum alveolar concentration (MAC) of 1. One gram of intravenous paracetamol was administered to all patients after induction of anaesthesia. Intra-operative HR, systolic blood pressure, diastolic blood pressure, mean arterial pressure, pulse oximetry and ECG were monitored every 5 minutes.

Immediately after induction, with the patient in supine position the upper limb on the side to be blocked was abducted to 90 degrees. Prior to the procedure, 2% chlorhexidine solution with 70% isopropyl alcohol was used to disinfect the skin and allowed to dry. A sterile ultrasound conducting gel was applied to the skin and the transducer probe of the ultrasound machine. A condom probe cover was then applied on the transducer probe. Before and after each procedure, the ultrasound apparatus was appropriately cleaned and disinfected with disinfectant wipes and allowed to air dry. The probe of a Butterfly iQ ultrasound machine (Butterfly Network, Guilford, Connecticut, USA) was placed over the mid-clavicular region of the thoracic cage in a sagittal plane. The ribs were counted inferiorly and laterally, until the fifth rib was identified in the midaxillary line. The latissimus dorsi (superficial and posterior) and the serratus anterior muscles (deep and inferior) were then identified by ultrasound overlying the fifth rib.

A 100mm 22-gauge sonovisible block needle (B.Braun, Germany) was introduced in the fascial plane between the posterior border of the serratus anterior muscle and the surface of the 5^{th} rib using an in plane technique. Confirmation of correct needle position was done by injecting 1-2ml of 0.9% normal saline. After negative aspiration of blood, 0.4ml/kg of the injectate was administered. Frequent intermittent aspiration was done after delivering 3-5mls of injectate to avoid intravascular injection. Adequate spread was noted deep to the serratus anterior muscle

and above the border of the rib and usually separating the serratus anterior muscle from the external intercostal muscle. The deep serratus anterior plane block technique was adopted because it is an easier technique as the rib serves as a reference point for injection and also it potentially facilitates blockade of higher-order lateral cutaneous intercostal nerves.

Patient's vitals were noted immediately after administering the block, at skin incision, 30 minutes and one hour after surgical skin incision and anytime there was an intervention. The mean arterial pressure and heart rate were the principal parameters used to guide intraoperative analgesia management. Heart rate and mean arterial blood pressure (MAP) were maintained within 20% of the preoperative baseline values by giving intravenous (IV) bolus doses of 1-2mg of morphine when the MAP or heart rate increased more than 20% from the baseline values as a result of pain. Ephedrine 5 mg boluses was given IV as needed to keep MAP greater than 65 mm Hg. Also, atropine 0.5 mg was given IV for heart rate less than 50 beats per minute.

At the end of surgery, patients were extubated fully awake and sent to the recovery ward/post anaesthesia care unit (PACU). Upon arrival at the recovery ward, postoperative pain was assessed as soon as patient was fully conscious and communicating and at 1, 4, 8 and 24 hours after the operation. The Numerical Rating Scale was used to assess pain in these patients. (NRS:0=no pain to 10=worst imaginable pain). NRS was explained to the patients during the preoperative assessment. Verbally administered NRS was used because it has been found to be a good tool for assessing acute pain.[185]

Postoperative pain management for all the patients was standardized. Patients with NRS greater than 5 who were still in the recovery/PACU received intravenous morphine 1-2mg bolus repeated at 5 minutes intervals until the NRS was 3 or less. Intramuscular Pethidine 1-2mg/kg was given to patients who have been sent to the ward and scored NRS more than 5. One gram of intravenous paracetamol 6 hourly was prescribed for all patients.

The total amount of Morphine and Pethidine administered in a 24-hour period was recorded. Patient satisfaction with pain management was also assessed 24 hours postoperatively, using a simple questionnaire after.

3.7 Ethical considerations

3.7.1 Approval

The study was approved by the Dissertation Review Committee of the Ghana College of Physician and surgeons and the Korle Bu Teaching Hospital Institutional Review Board (KBTH-IRB) (see appendix).

3.7.2 Postoperative analgesia

For postoperative analgesia, all patients recruited for this study received IV paracetamol 1g 6 hourly and were written up to receive IV morphine 1-2mg prn whiles in the recovery/PACU and IM pethidine 1-2mg/kg prn whiles on the ward.

3.7.3 Local anaesthetic systemic toxicity (LAST)

One potential problem that was anticipated during this study was LAST. This was prevented by using doses of local anaesthesia well below the minimum recommended dose for any individual. Lipid emulsion (20% intralipid) was made available, in the unlikely event that a local anaesthetic systemic toxicity occurred.

3.7.4 Informed consent

Participation in this study was absolutely voluntary. All patients who met the inclusion criteria were given detailed information on the purpose, nature, procedures and potential risks of the study. Participants were at liberty to withdraw from the study at any time. Refusal to participate or withdrawal from the study did not affect their clinical management. After agreeing to participate they were required to sign or thumbprint on a consent form (Appendix 2)

Information and data obtained from this study was kept strictly confidential and under lock and key. There was no remuneration to the study participants since the study was not externally funded. The cost of the ultrasound, peripheral nerve stimulator and the study medication (plain bupivacaine) was borne by the principal investigator.

3.8 Data Handling

3.8.1 Data collection tools

A self-designed data extraction form(appendix) was used to collect the data.
Data collected included:

1. Patient's demographics: Age, sex, weight, height, BMI, ASA
2. Diagnosis and surgical procedure performed
3. Neoadjuvant chemotherapy given
4. Comorbidities
5. Surgery start and end times
6. Pre-induction and post-induction heart rate (HR), NIBP, oxygen saturations (SpO_2) and respiratory rate (RR)
7. Vitals (HR, NIBP, SpO_2, RR) after serratus anterior block is given
8. Vitals (HR, NIBP, SpO_2, RR) at the time of incision, 30 minutes and one hour after incision
9. NRS when patient was fully awake and at 1, 4, 8 and 24 hours.
10. Vitals (HR, NIBP, SpO_2, RR) at 1, 4, 8 and 24 hours postoperatively
11. Total opioid (morphine equivalent) consumed intraoperatively and postoperatively
12. Presence of PONV
13. Patient satisfaction

3.8.2 Data entry

Data collected was entered into a Microsoft Access database by two research assistants. Source document verification was done to ensure accurate and credible data. Data of participant who after being recruited into the study were lost to follow up were censored for removal from data analysis. Participants included in the study were assigned unique but confidential identifiers.

3.9 Statistical Data Analysis

3.9.1 Data analysis

Data obtained was exported into and analysed using IBM Statistical Package for Social Sciences (SPSS) version 25.

The key to the codes for the groups (X and Y) was only revealed to the principal investigator by the supervisor having the key, after data collection and analysis. The code was X (0.25% plain bupivacaine/Intervention group) and Y (0.9% normal saline/Control group).

3.9.2 Parameters of interest

The parameters of interest were NRS score of patients postoperatively, incidence and severity of postoperative pain, total amount of opioid consumed perioperatively, incidence of postoperative nausea and vomiting and the level of patient satisfaction with postoperative analgesia.

3.9.3 Data presentation

Continuous variables were summarized using means and standard deviations whilst proportions and percentages were used to describe categorical variables. Incidence was expressed as percentages. A repeated measure Analysis of Variance (ANOVA) was used to compare the means of continuous variables such as systolic arterial blood pressure, diastolic arterial blood pressure, mean arterial pressure, heart rate and respiratory rate, measured intraoperatively and postoperatively between the two groups. Also, an independent t test was used to compare the means of continuous variables such as age, weight, height, BMI, systolic and diastolic blood pressures, MAP, HR, total opioid (morphine equivalent) consumed, between the two groups. Pearson's Chi square test of independence and Fisher's exact test were used to compare categorical variables such as severity of NRS (NRS<5 regarded as mild pain, NRS 5-7 considered as moderate pain, NRS>7 severe pain) in both the control and intervention group. A *p value* less than 0.05 was considered as statistically significant.

CHAPTER 4: RESULTS

4.1 CONSORT Diagram

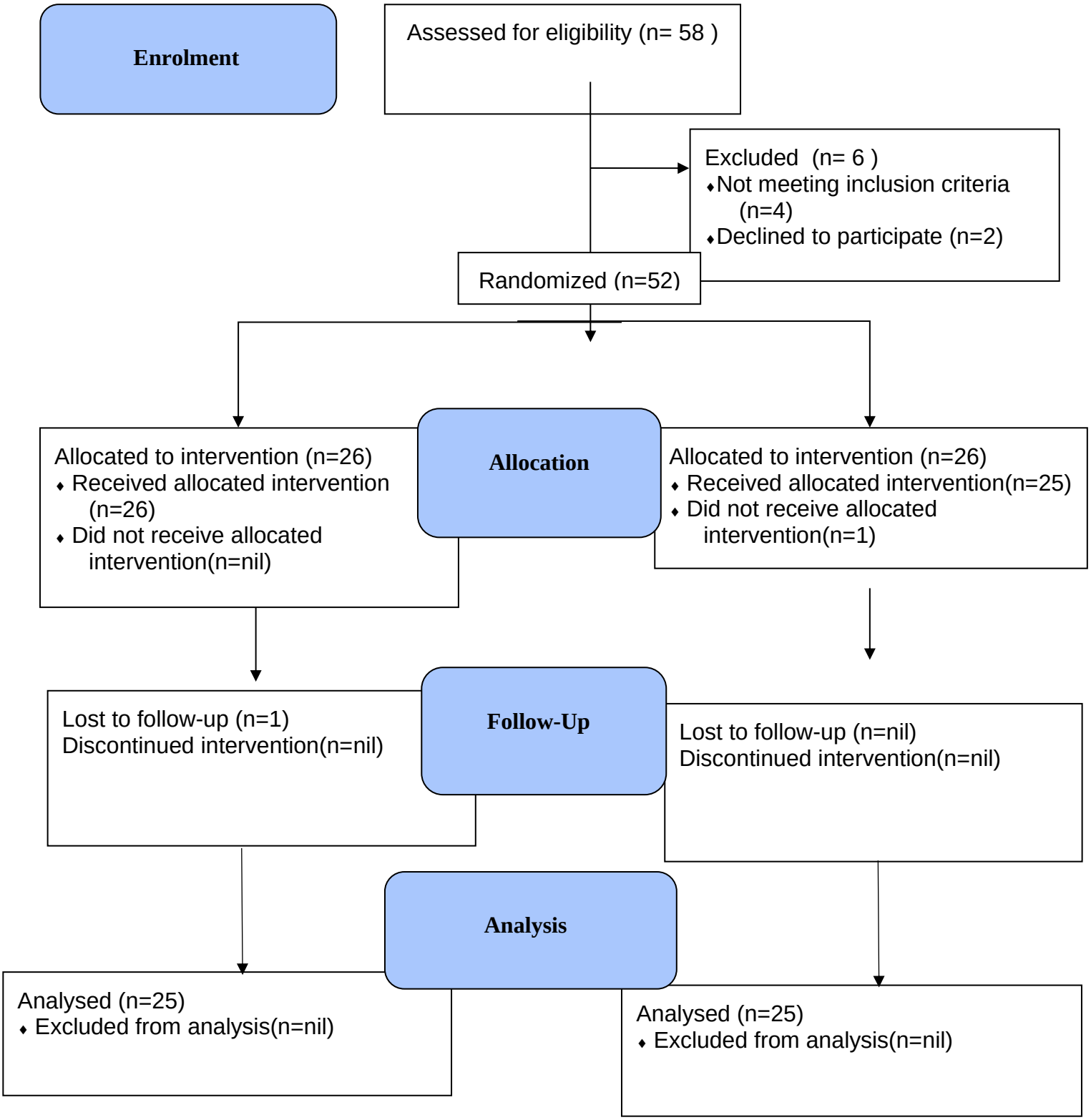

Figure 4.1: Consort diagram showing allocations of patients in the two study groups

A total of fifty-eight participants were enrolled into the study, however four of them were excluded because they did not meet the inclusion criteria. Two opted out on account of personal reasons. Twenty-six patients in the intervention group eventually received the allocated intervention. Outcome data was incomplete for one patient in the intervention group, leaving twenty-five patients for whom completed data was available to be analysed. In the control group, one patient opted out of the study in the morning of surgery citing personal reasons, leaving 25 patients who received the allocated intervention as shown in the consort diagram above. In this study there were 25 participants in the intervention (bupivacaine) arm and 25 patients in the control (saline) arm. The case: control ratio was thus 1:1.

4.2 Demographic characteristics

The study participants were mainly female, 49 (98%) with only 1(2%) being male. Therefore, the male:female ratio was 1:49.

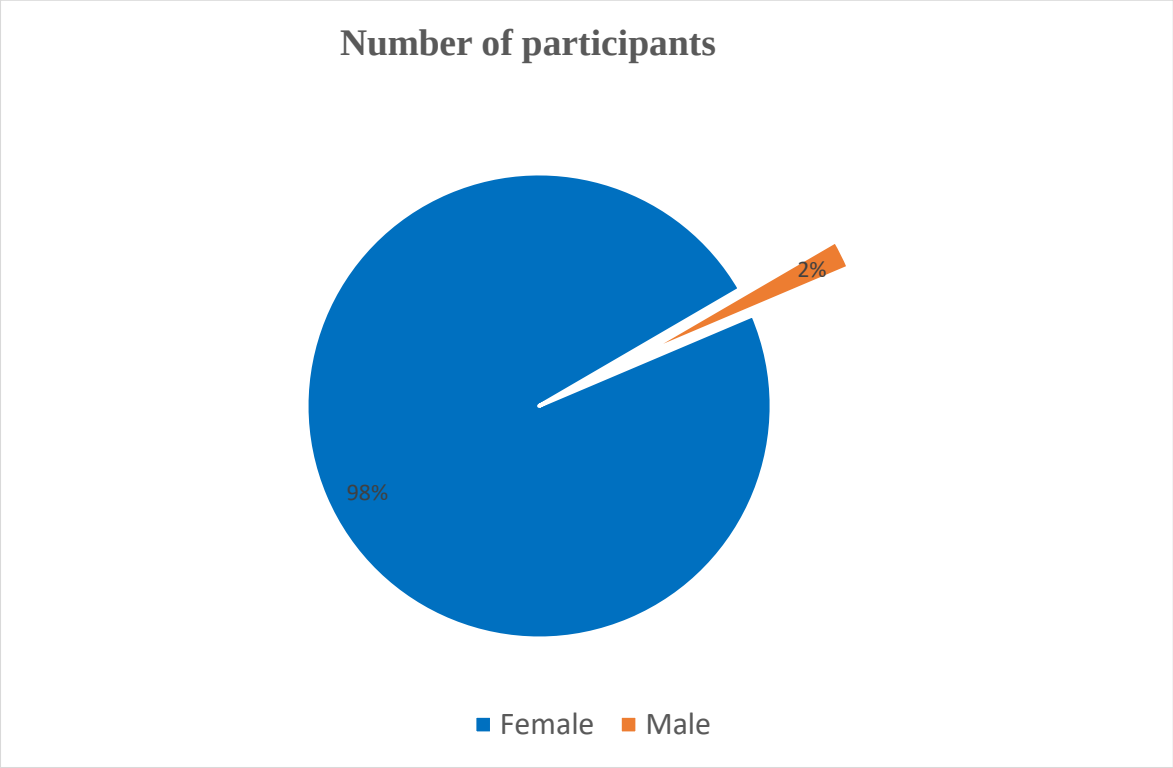

Figure 4.2: Gender distribution of participants

Their ages ranged from 19 to 70 years with a mean of 47.02±13.67 years. Majority of the participants (42%) were between 50 and 70 years. The mean age of the intervention group was 46.9±13.2 years and that for the control group was 47.2±14.4 years. There was however no statistically significant difference between the mean ages of these two groups (*p-value* = 0.943) as shown in figure 4.3 below.

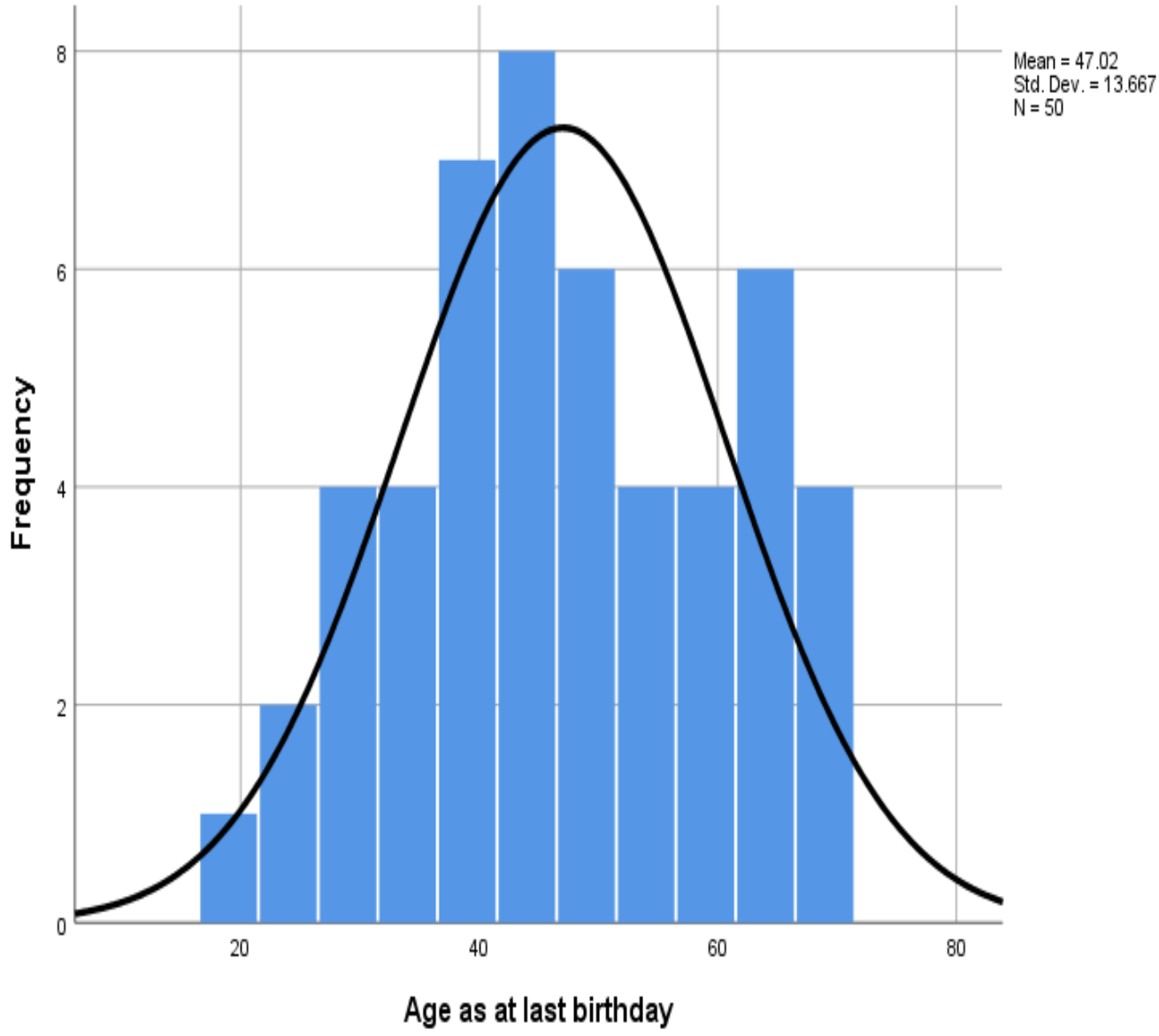

Figure 4.3: Age distribution of participants

The height of the participants ranged from 1.46 to 1.74 metres in the two groups. The mean height for the intervention group was 1.61±0.06 m and that for the control group was 1.62±0.07m. There was no statistically significant difference between the two groups (*p-value* =0.628) as shown in figure 4.4 below

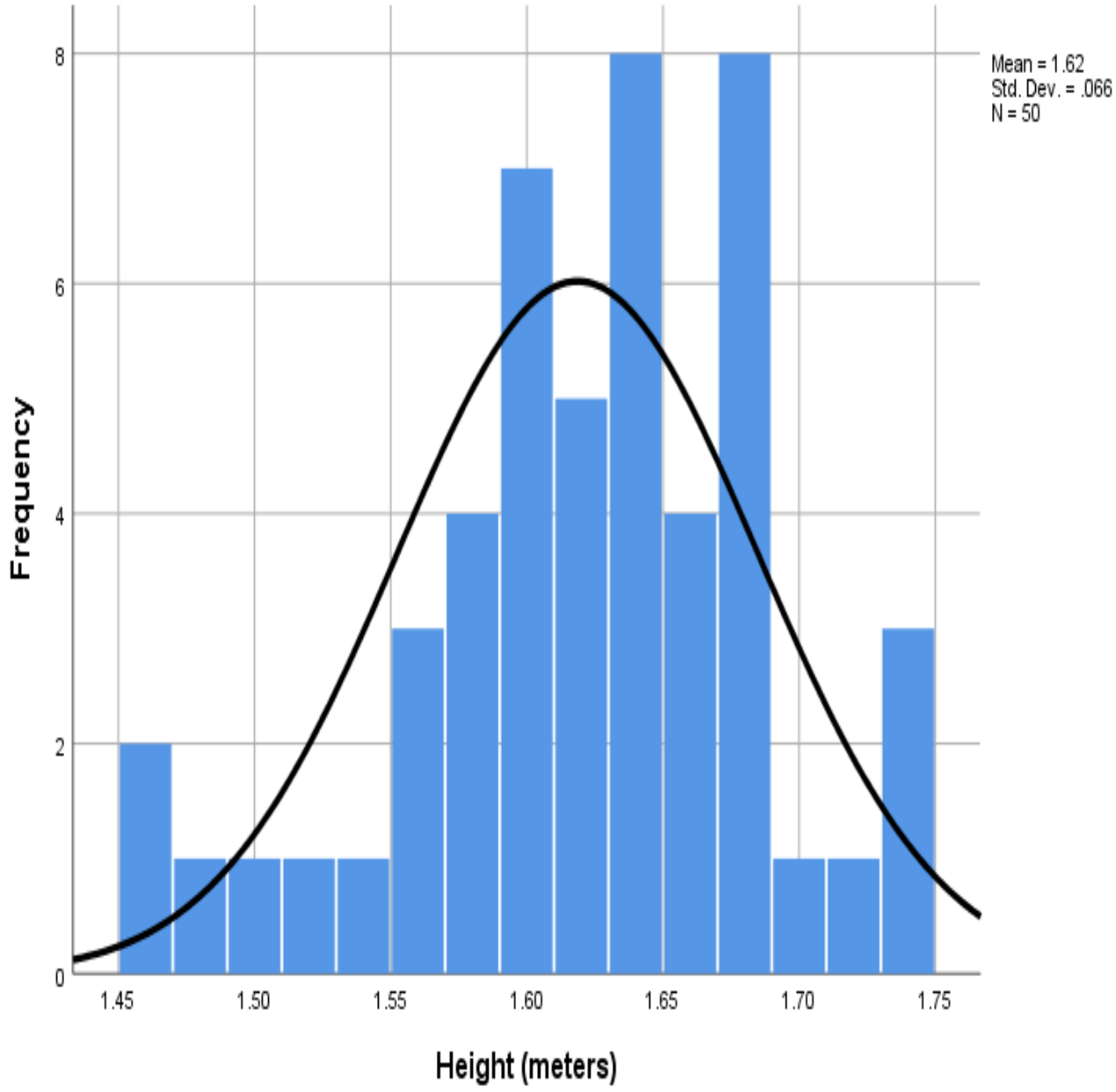

Figure 4.4: Height distribution of participants

The weights in the two groups ranged from a minimum of 31kg to a maximum of 100kg. The mean weight of the intervention and control groups were 72.1±16.7kg and 76±13.8kg kg respectively. There was however no statistically significant difference in the weight distributions of the study groups (*p-value* =0.373) as shown in figure 4.5 below.

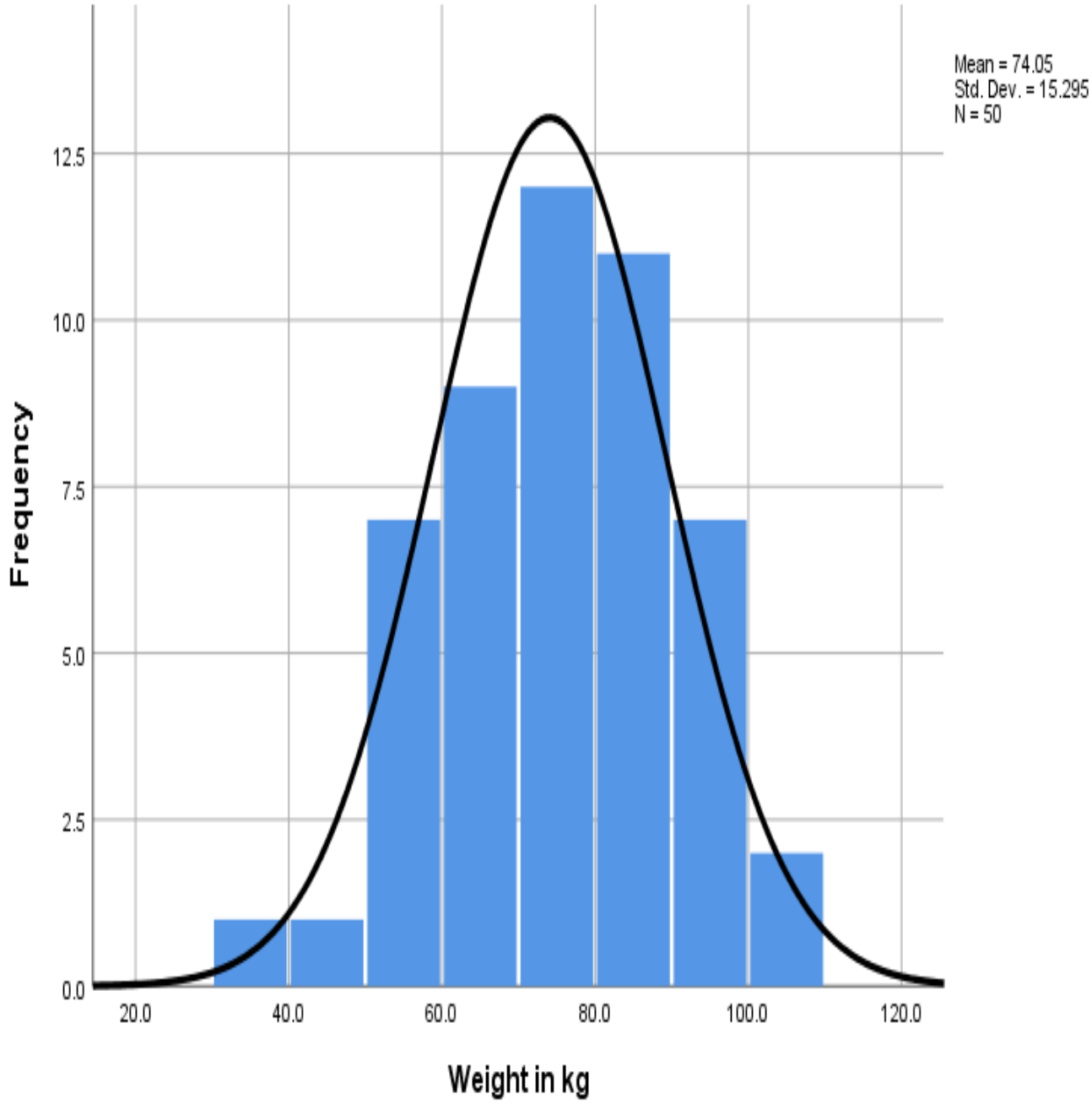

Figure 4.5: Weight distribution of participants

There was no statistically significant difference in the body mass index distribution of patients in the intervention and control groups with mean BMI of 28.1±4.6 kg/m^2 and 28.5±4.6 kg/m^2, respectively (*p-value* = 0.728) as shown in figure 4.6 below

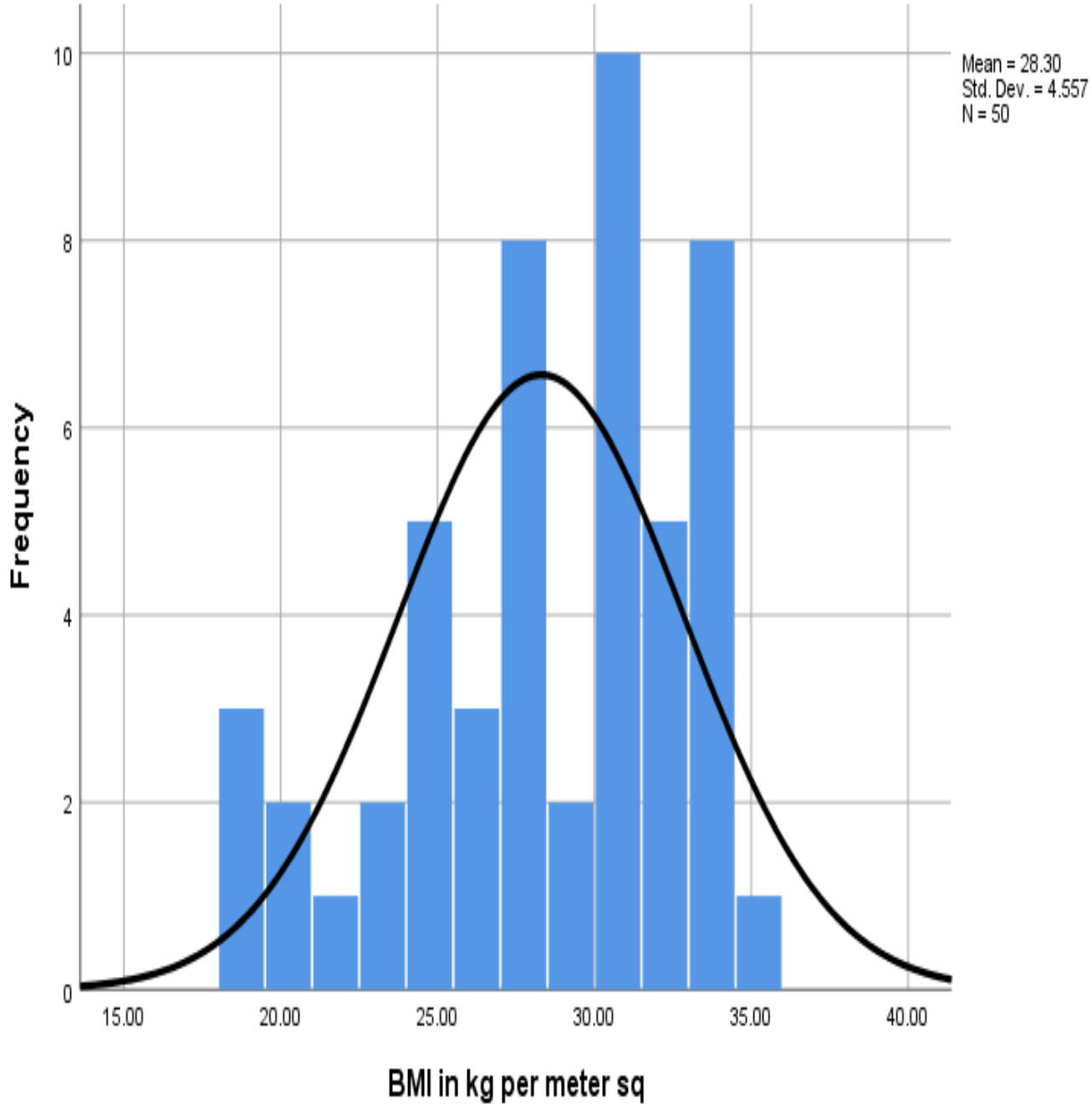

Figure 4.6: Body Mass Index distribution of participants

The descriptive summary of the age, weight, height and BMI is shown in the table below (Table 4.1). The two groups were comparable in age, weight, height and BMI with no statistically significant difference between them.

Table 4.1: Age, Height, Weight and BMI between the two groups

Demographic parameter	**Range**	**Groups: Mean ±SD**		**t-test**	**p-value**
		Intervention	**Control**		
Age(years)	19-70	46.9 ± 13.2	47.2. ±14.4	0.07	0.943
BMI (kg/m^2)	18-35	28.1±4.6	28.5±4.6	0.35	0.728
Weight(kg)	31-100	72.1± 16.7	76±13.8	0.90	0.373
Height(m)	1.46-1.74	1.61±0.06	1.62±0.07	0.49	0.628

4.3 Comorbidity

The commonest comorbidity among participants was hypertension. Twenty-three patients out of 50 patients were receiving treatment for hypertension. However, there were more patients in the control group with hypertension than there were in the intervention group but the difference between the two group was not statistically significant (*p-value* =0.777) as shown in Table 4.2 below

Table 4.2: Comorbidity between the two groups

Comorbidity	**Levels**	**Group: n (%)**		**Chi-square test**	***p*-value**
		Intervention	**Control**		
Hypertension	Yes	11 (44.0)	12(48.0)	0.08	0.777
	No	14 (56.0)	13(52.0)		
Diabetes	Yes	2 (8.0)	3(12.0)	0.22	0.637
	No	23(92.0)	22 (88.0)		
Asthma	Yes	0(0.0)	1(4.0)	1.02	0.312
	No	25(100)	24(96.)		
Others		2(8.0)	2(8.0)	3.74	1.000

4.4 ASA Status

All participants in this study were either ASA physical status I or II. The intervention group, formed the majority in ASA I physical status. Whilst in ASA II physical status, the control group had slightly higher representation, as shown in Table 4.3 below. These differences in the distribution were, however not statistically significant with a *p-value* of 0.370.

Table 4.3: ASA status of participants

ASA Status	**Group: n(%)**		**Chi-square test**	***p*-value**
	Intervention	**Control**		
I	10 (40.0)	7 (28.0)	0.80	0.370
II	15 (60.0)	18 (72.0)		

4.5 Indication for surgery

The main indication for breast surgery in this study was breast cancer. Forty-three (22 intervention case and 21 controls cases) patients representing 86% had breast cancer. The remaining diagnosis comprised of duct ectasia, intraductal papilloma, phylloides tumour, and accessory breast. A Fisher's exact test conducted showed no statistically significant difference (*Fisher's-test* =4.88, *p-value* =0.853) in the diagnosis of patients in the intervention group compared with those in control group as shown in the Table 4.4 below

Table 4.4: Indication for surgery

Diagnosis	**Group: n(%)**		**Fisher's exact test**	**p-value**
	Intervention	**Control**		
Accessory breast	0(0.0)	1(4.0)	4.88	0.853
Lt Breast Ca	11(44.0)	8(2.0)		
Rt Breast Ca	11 (44.0)	11(44.0)		
Lt duct ectasia	1(4.0)	1(4.0)		
Lt intraductal papilloma	1(2.0)	0(0.0)		
Rt Intraductal papilloma	0(0.0)	1(4.0)		
Phyllodes tumour	1(4.0)	2(8.0)		
Suspicious Rt Breast lump	0 (0.0)	1(4.0)		

4.6 Type of Surgery

There was no significant difference in the type of surgery performed when the two groups were compared as shown in Table 4.5 below (*Fisher's exact test =5.86, p-value =0.458).*

Table 4.5: Type of Surgery

Type of Surgery	**Group: n (%)**		**Fisher's exact Test**	***p*-value**
	Intervention	**Control**		
Mastectomy + ALND	16 (64.0)	15 (60.0)	5.86	0.458
WLE	0(0.0)	3 (12.0)		
Excision Biopsy	1(4.0)	2 (8.0)		
Mastectomy	1(4.0)	1(4.0)		
Hadfields	1(4.0)	2(8.0)		
WLE + ALND	5(20.0)	2(8.0)		
Others	1(4.0)	0(0.0)		

4.7 Duration of Surgery

Majority of the surgeries lasted more than 2 hours. There was no statistically significant difference between the two groups with regards to the duration of surgery as shown by a *p-value* of 0.569.

Table 4.6: Duration of surgery

Duration of surgery	**Groups:n (%)**		**Fisher's exact Test**	**p-value**
	Intervention	**Control**		
<1hr	0(0.0)	0 (0.0)	0.33	0.569
1-2hrs	12(48.0)	10(40.0)		
>2hrs	13(52.0)	15(60.0)		

4.8 Neoadjuvant Chemotherapy

In this study, thirty-two patients received neoadjuvant chemotherapy before coming for their surgery with four more patients in the intervention group than in the control group having received neoadjuvant chemotherapy. The difference was however not statistically significant (*p-value* = 0.239).

Table 4.7: Neoadjuvant chemotherapy

	Response	**Groups:n (%)**		**Chi-square test**	***p*-value**
		Intervention	**Control**		
Neoadjuvant chemotherapy	**Yes**	18(72.0)	14(56.0)	1.39	0.239
	No	7(28.0)	11(44.0)		

4.9 Intraoperative Systolic Blood Pressure

The mean intraoperative systolic blood pressure of the intervention group was lower than that of the control group, however, there was no significant difference between the two groups as shown in Figure 4.7 below (F-test = 0.13: *p-value* = 0.719)

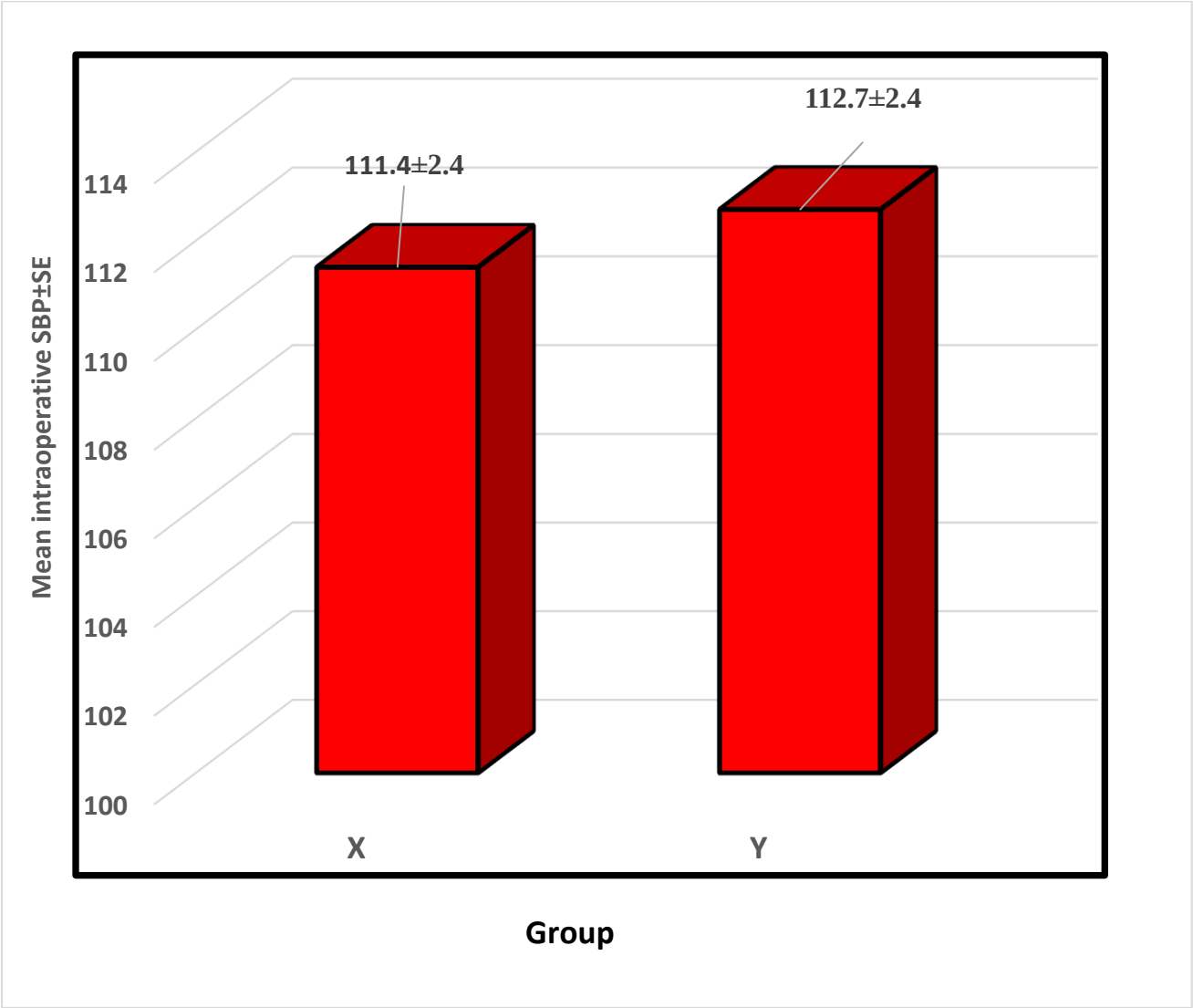

Figure 4.7: Intraoperative Mean SBP between the two groups

There was a general decline in the measured intraoperative mean systolic blood pressures of both groups. However, the difference between the two groups was not statistically significant at the various time points, though the mean SBPs of the control group were slightly higher than the intervention group (*F-test* =0.13: *p-value* =0.719) as shown in Figure 4.8 below

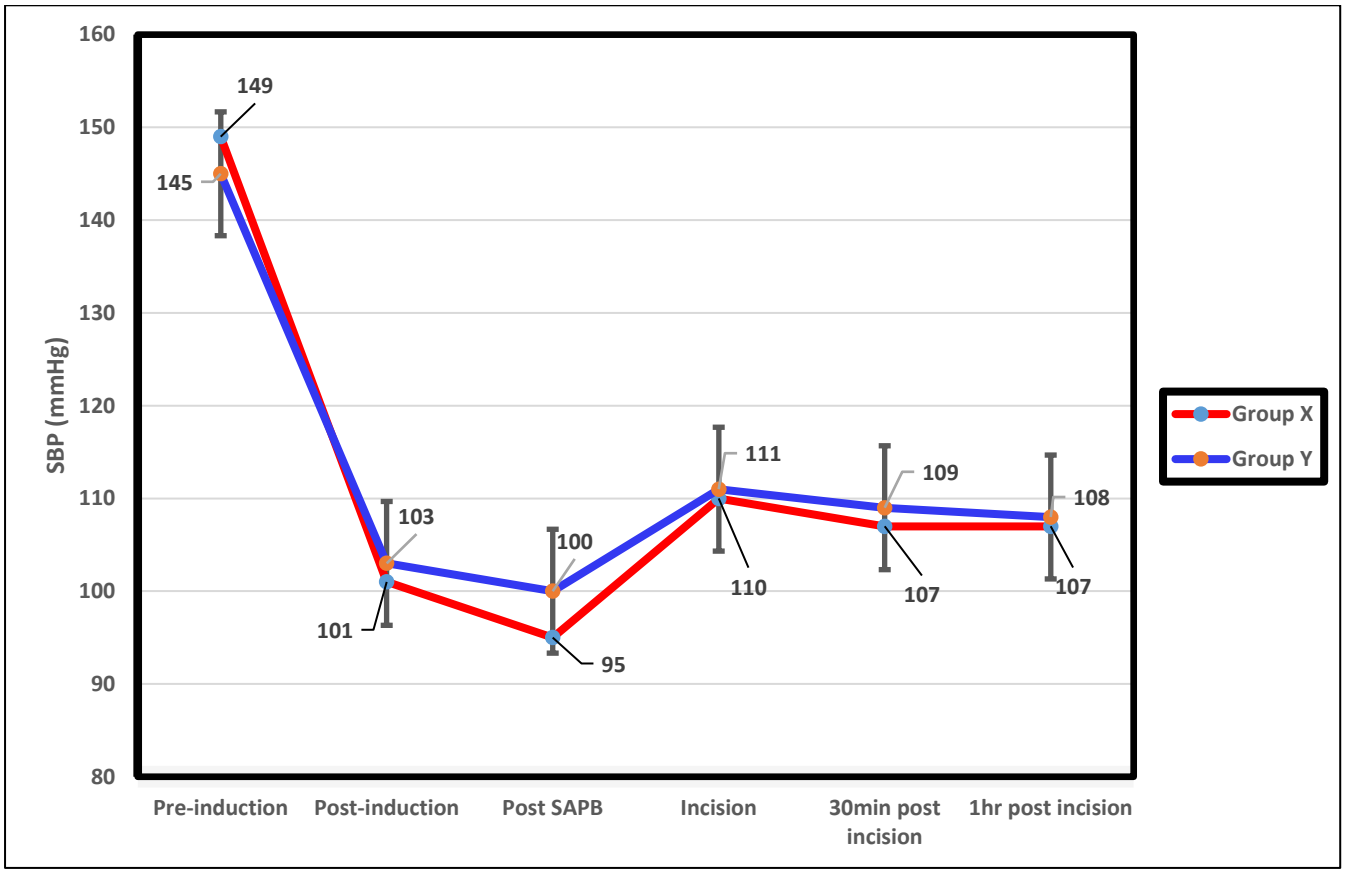

Figure 4.8: Time series plot of Intra-operative systolic blood pressure

4.10 Intraoperative Diastolic Blood Pressure

It was found that although the intraoperative mean diastolic blood pressure (DBP) in the intervention group was higher than that of the control group, the difference was not statistically significant (F-test=1.06: *p-value* =0.308) as shown in Figure 4.9 below.

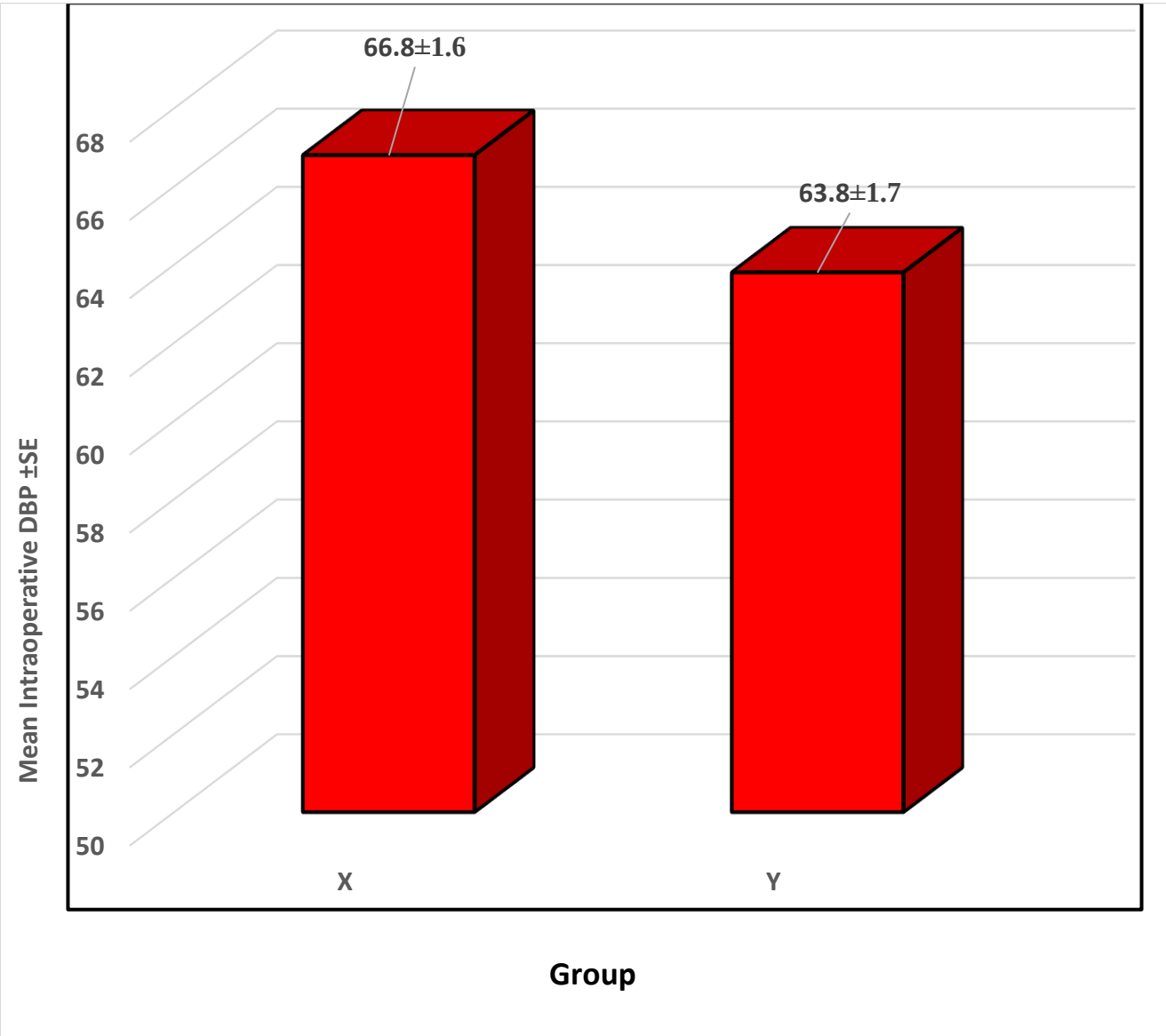

Figure 4.9: Intraoperative Mean DBP between the groups

The intraoperative mean diastolic blood pressure decreased with time in both groups. The diastolic blood pressures of the intervention group were slightly higher than that of the control group except at 30 minutes post incision. There was however no statistically significant difference between the two groups at the different time points (*F-test* =1.06; *p-value* =0.38).

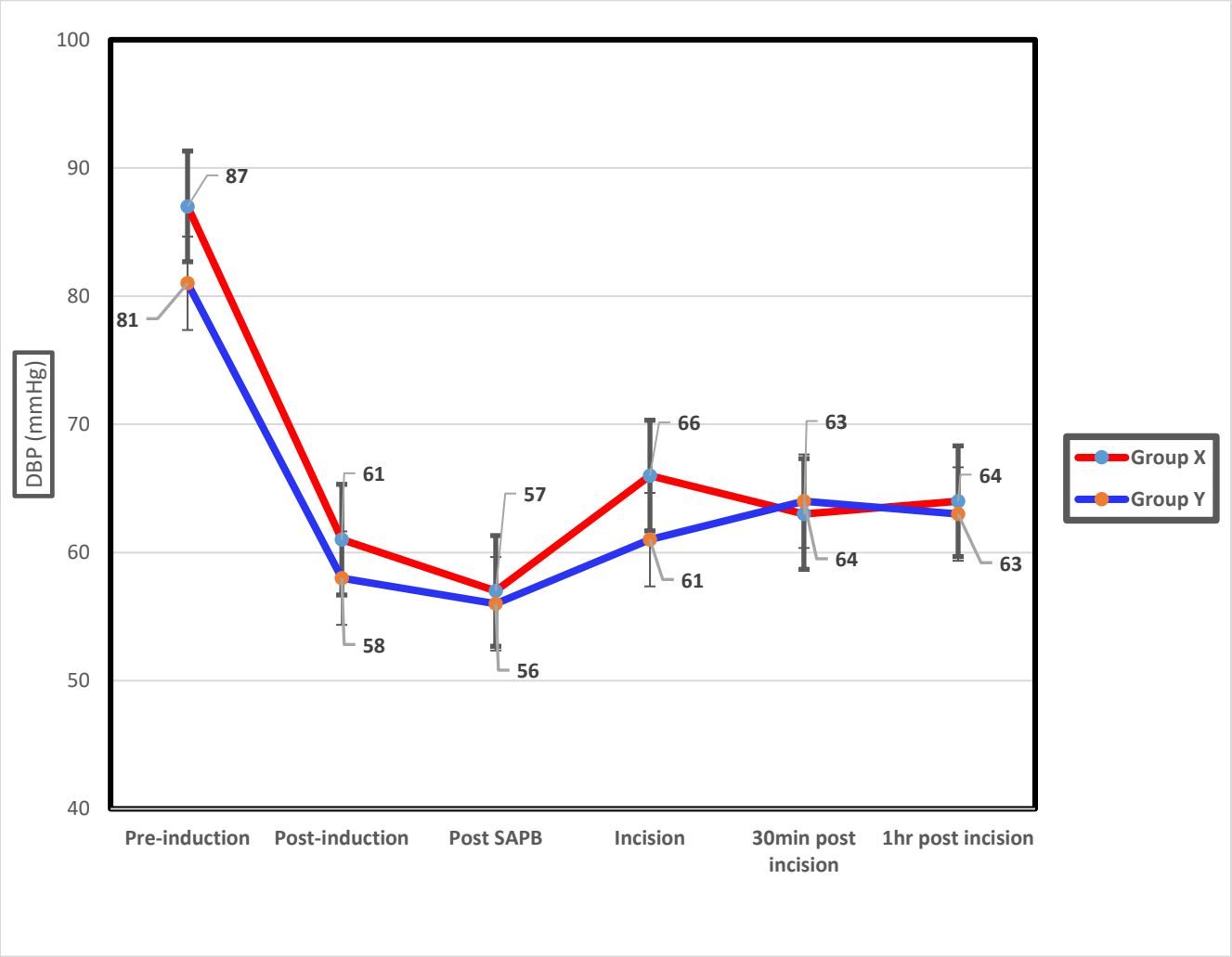

Figure 4.10: Time series plot of Intra-operative diastolic blood pressure

4.11 Intraoperative Mean Arterial Pressure

Figure 4.11 shows that the intraoperative mean MAP of the intervention group was slightly higher than that of the control group however, the difference between the two groups was not statistically significant (F-test = 0.43: *p-value* = 0.515)

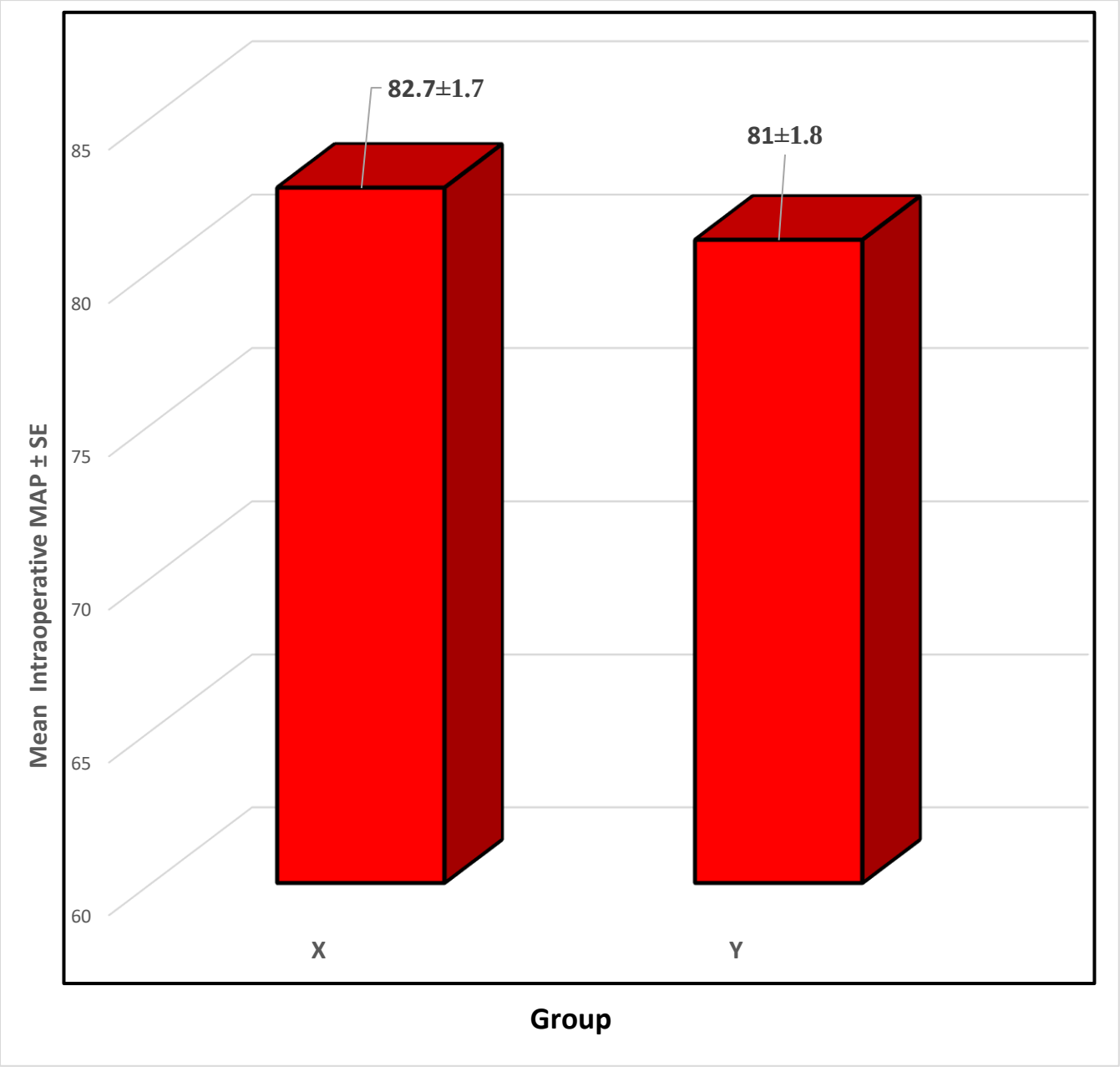

Figure 4.11: Intraoperative Mean MAP between the two groups

Similarly, the intraoperative MAP of both groups declined after induction of anaesthesia and then increased slowly after skin incision and remained steady afterwards. There was no statistically significant difference between the two groups at the different time points as shown in the figure 4.12 below (*F-test* =0.45 *p-value* =0.755)

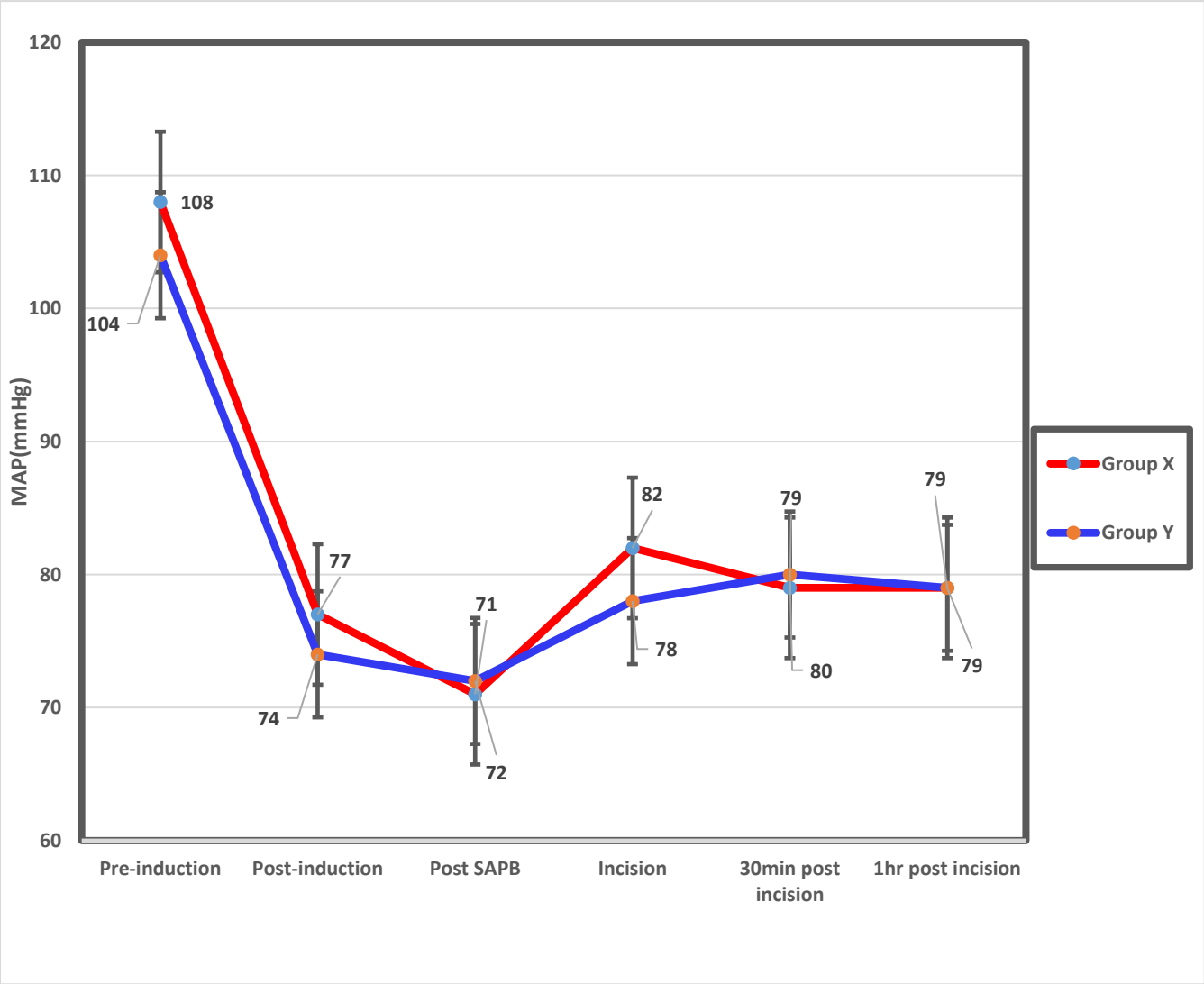

Figure 4.12: Time series plot of Intraoperative mean arterial pressure

4.12 Intraoperative Heart Rate

The mean intraoperative heart rate of the control group was higher than that of the intervention group. However, the difference between them was not statistically significant as shown in figure 4.13 (F-test = 0.28: *p-value* =0.560)

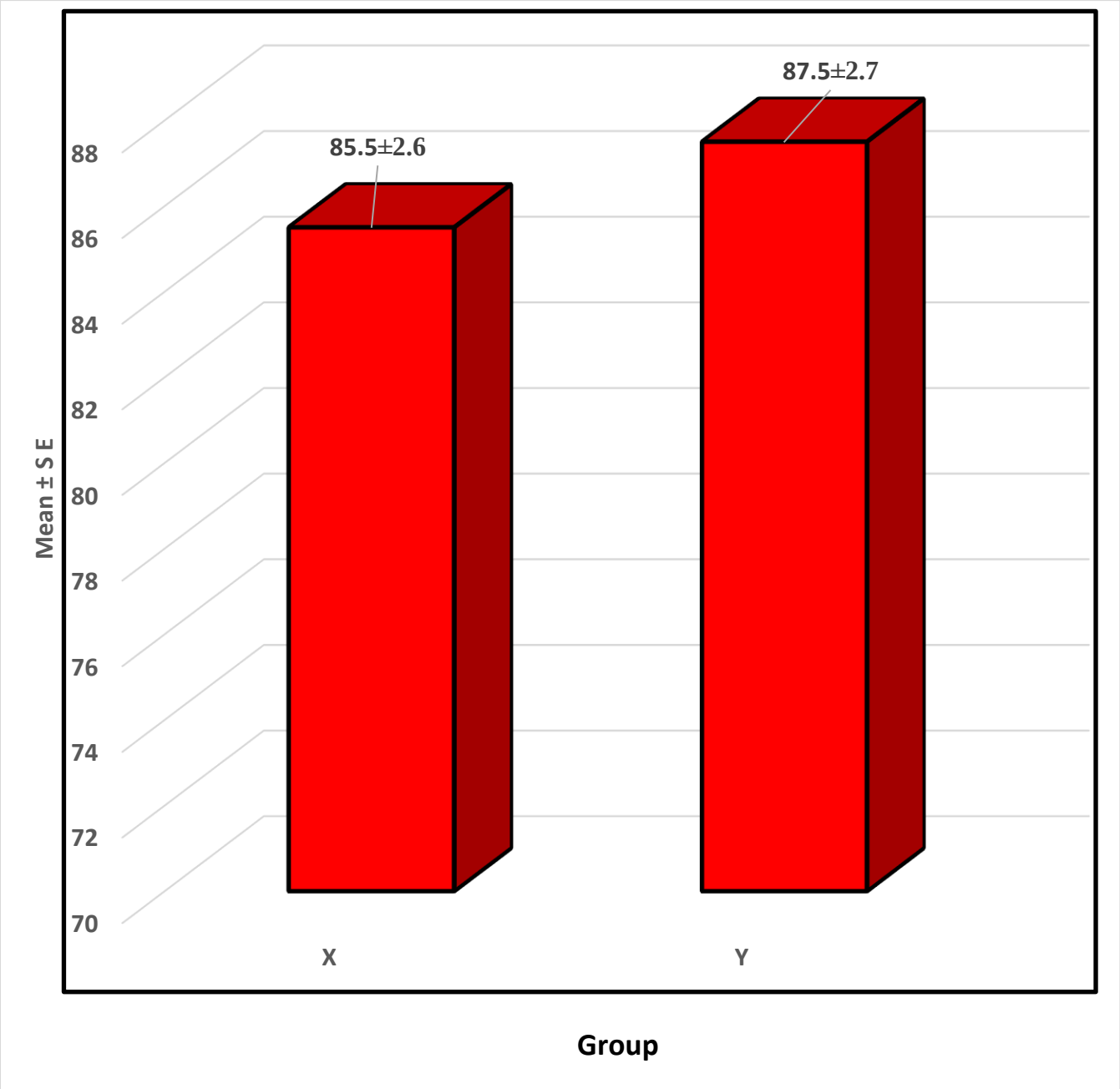

Figure 4.13: Intraoperative Mean HR between the two groups

The mean heart rates of both groups declined after induction, then increased gradually peaking after skin incision. There after the control group's heart rate remained high close to the preinduction heart rates. The mean heart rate of the intervention group on the other hand were lower compared to that of the control group after incision. However, the F-test conducted did not show statistically significant difference between the two groups at the various time points (*F-test* =0.28; *p-value* =0.592).

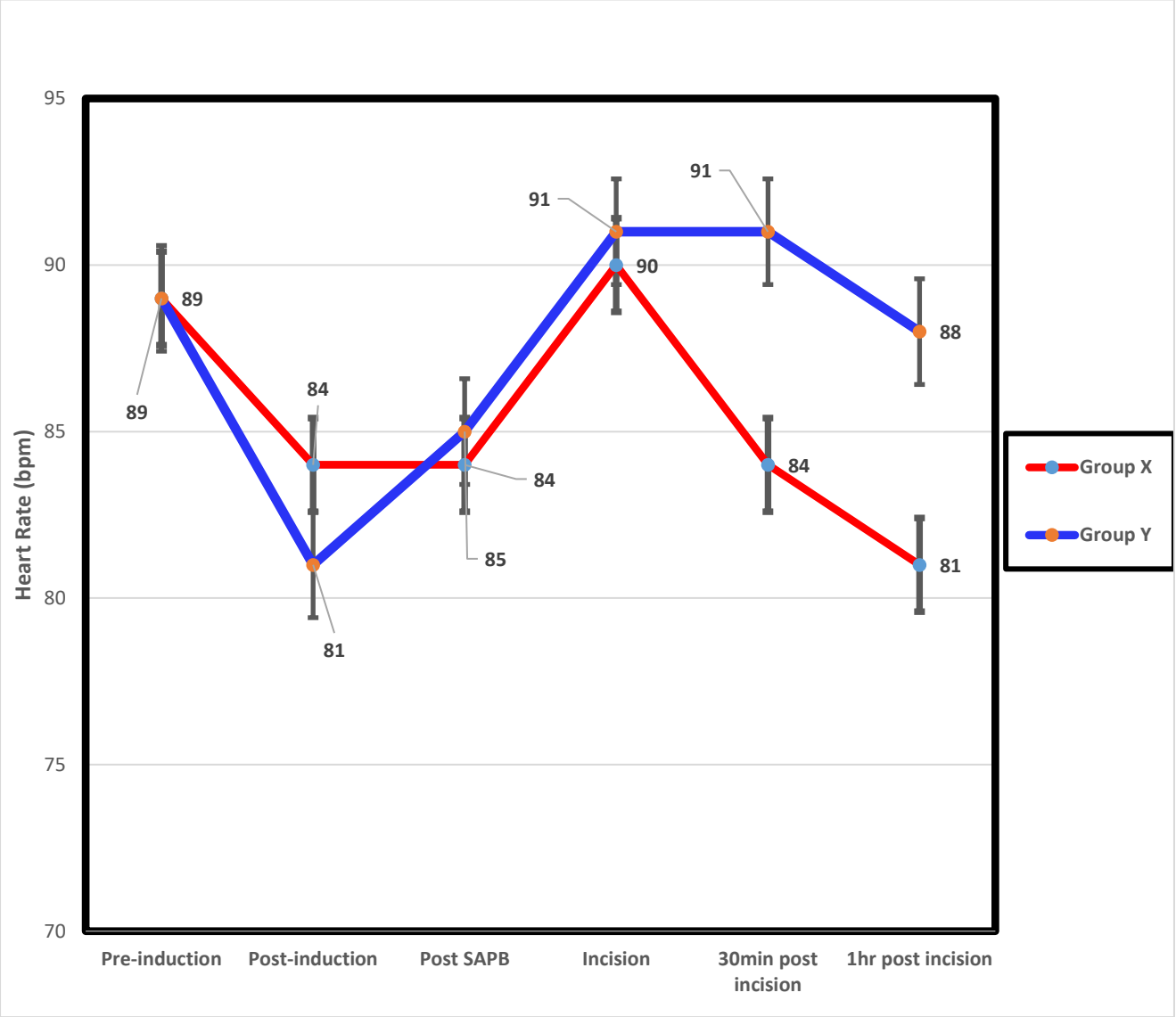

Figure 4.14: Time series plot of Intraoperative heart rate

4.13 Intraoperative Respiratory Rate

Figure 4.15 shows that intraoperative mean respiratory rate for the control group was comparatively higher than that of the intervention group, although the difference was not statistically significant (F-test=2.00; *p-value*=0.164).

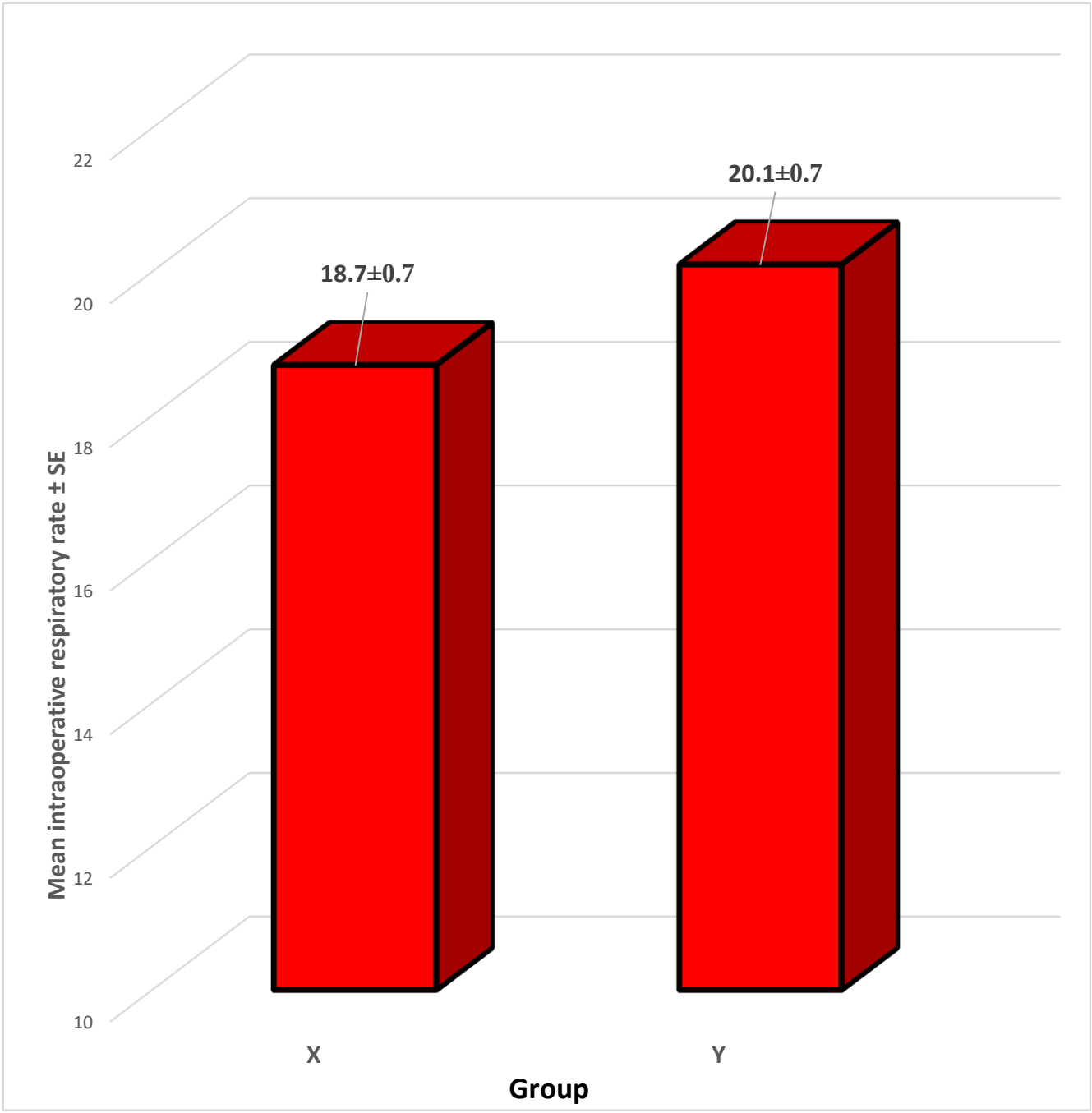

Figure 4.15: Intraoperative Mean Respiratory rate between the groups

In this study, the respiratory rate in both groups rose steadily from pre-induction to skin incision and then plateaued. The mean respiratory rate in the intervention group was slightly lower than that in the control group, however the difference was not statistically significant at the various time points as shown in figure 4.16 below.

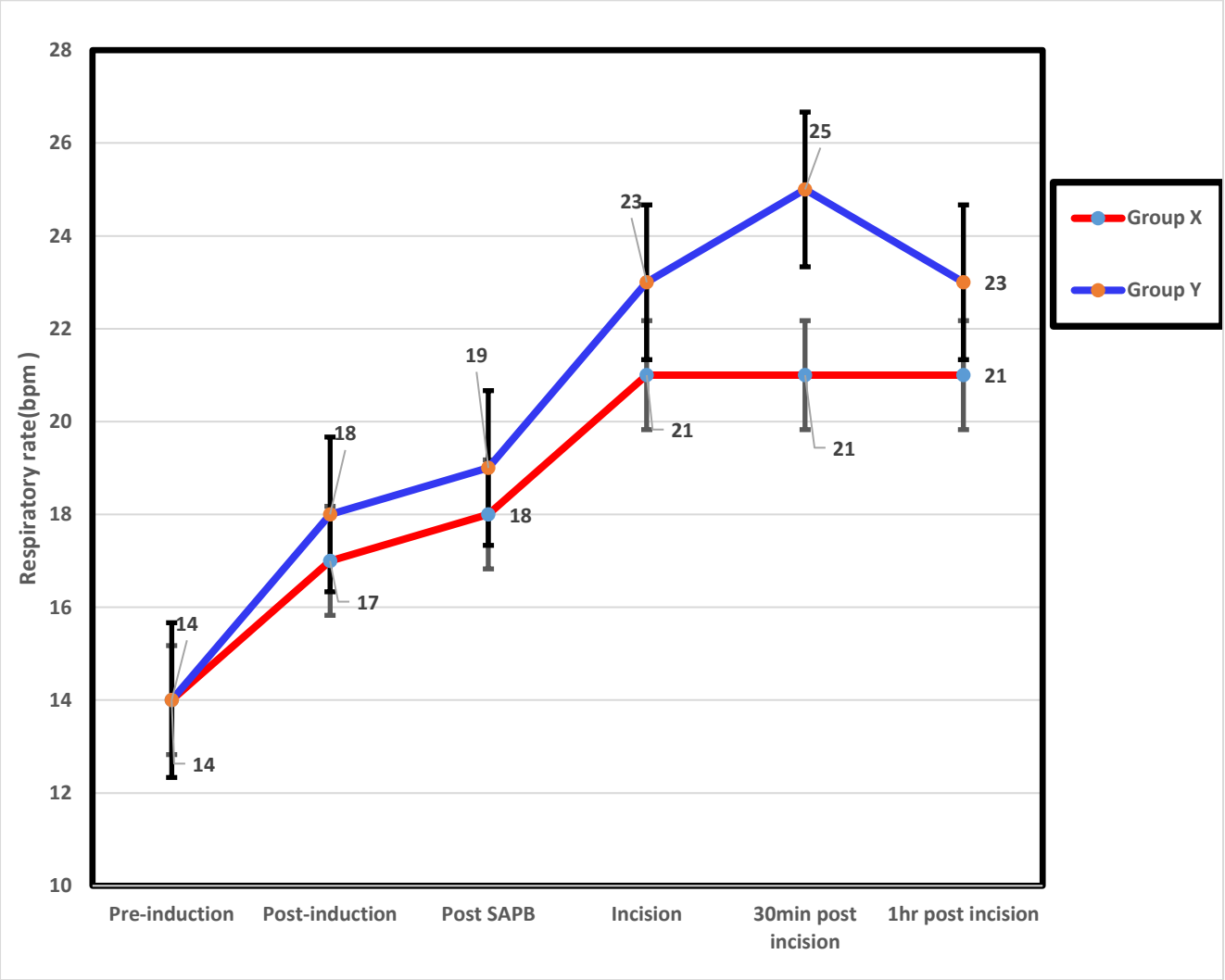

Figure 4.16: Time series plot of Intraoperative respiratory rate

4.14 Postoperative Numerical Rating Scale Score

In this study, the NRS for the intervention group declined from the first hour to the 24th hour and that for the control group initially increased from the first hour to the fourth hour then gradually declined. However, the decline in NRS at the various times between the two groups was not statistically significant (*F-test* =2.42; *p-value* =0.068)

NRS Score

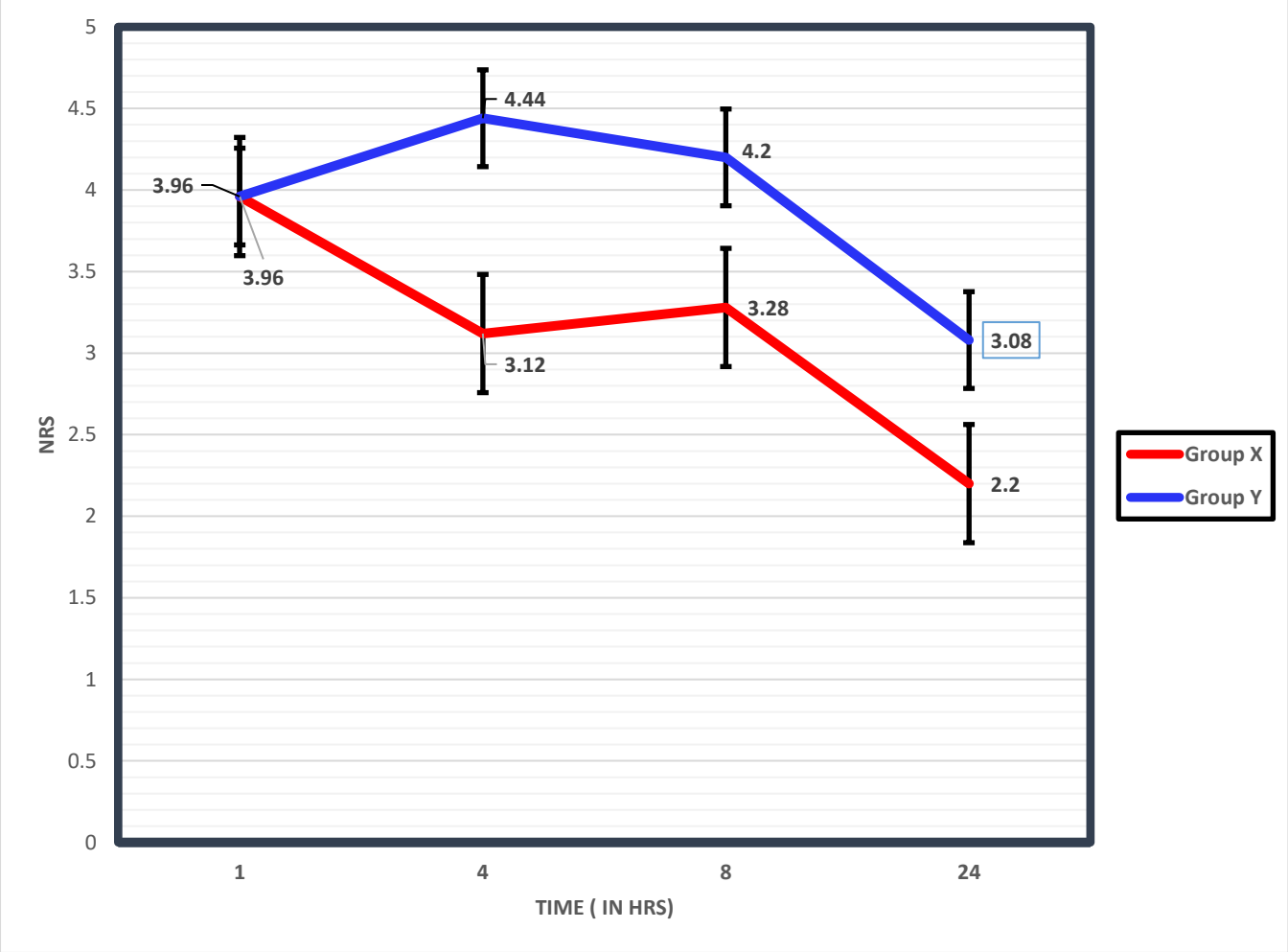

Figure 4.17: Time series plot of NRS scores

The mean NRS for the control group was significantly higher than that of the intervention group as shown in figure 4.18 below (F-test = 9.05: *p-value* = 0.004)

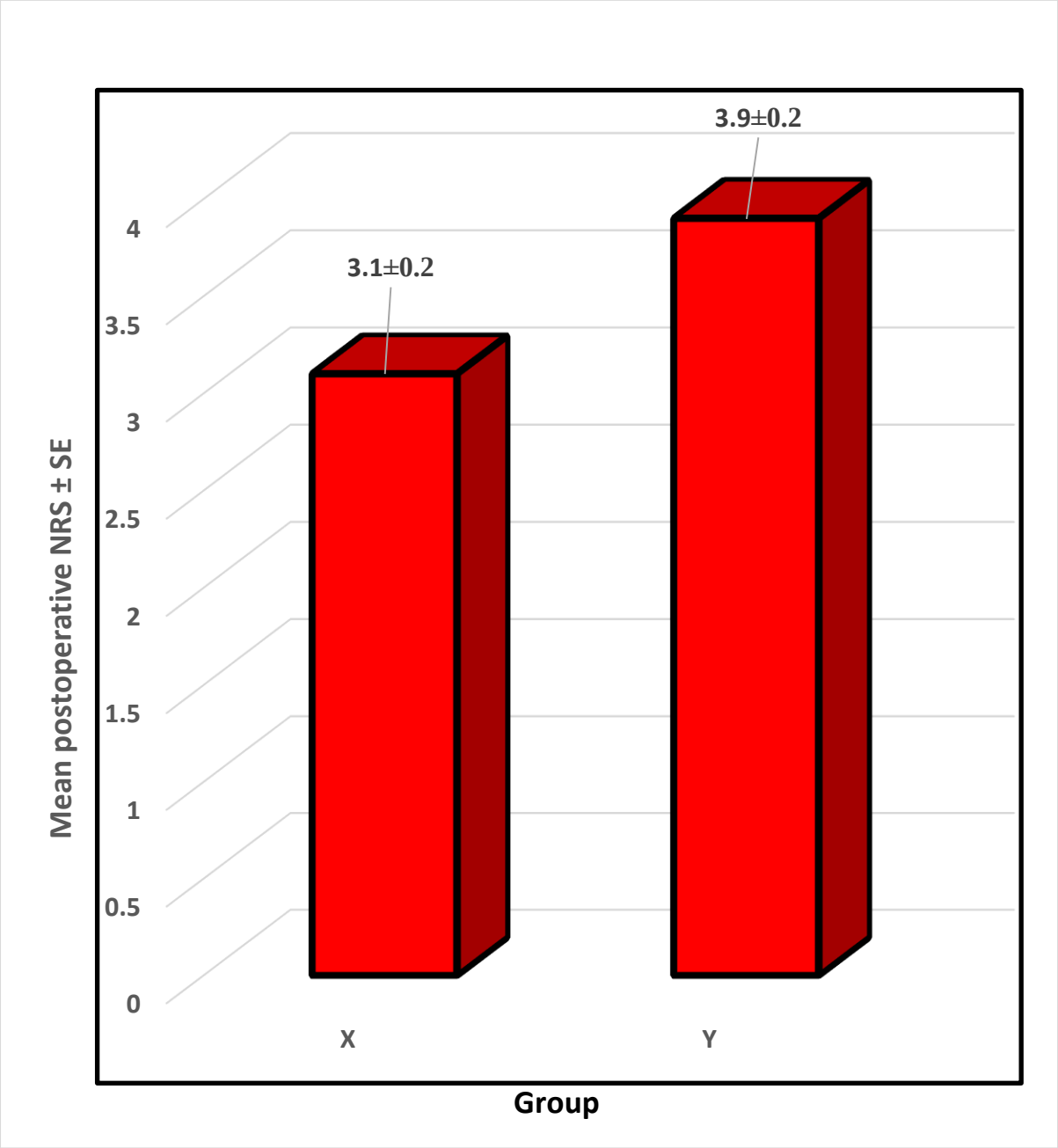

Figure 4.18: Postoperative mean NRS between the two groups

4.14.1 Incidence and severity of pain between the two groups

The incidence and severity of pain (reflected by the NRS score) between the two study arms at various time intervals are displayed in the table below.

In the first hour, 56% of patients in the intervention group had mild pain (defined as NRS ≤4), whereas 44% had moderate pain (defined as NRS 5 to 6). None of the participants in the intervention group had severe pain (defined as NRS ≥7). In the control group, 64% had mild pain and 32% registered moderate pain. Four percent of participants in the control group had severe pain.

A chi-square analysis of NRS at 1hour did not show any statistically significant difference between the two groups (*p-value* =0.448).

The NRS recorded at 4 hours showed mild pain in 92% of the intervention group compared to 52% in the control group. More participants in the control group, 48%, had moderate pain compared to 8% in the intervention group. No participant recorded severe pain at this hour. A Chi-square analysis showed statistically significant difference in NRS scores at this time (*p-value* =0.002).

At 8 hours, 80% of participants in the intervention group had mild pain, compared to 76% in the control group. 20% of participants in the intervention group had moderate pain compared to 24% in the control group. No participant experienced severe pain. There was no statistically significant difference in the severity of pain between the two groups measured at this hour. (*P-value* =0.733)

At 24 hours both study arms recorded only mild pain.

Table 4.8: NRS pain scores at different observation time points

Time	Category	Groups:n (%)		Chi-square test	*p-value*
		Intervention(%)	**Control (%)**		
NRS at 1 hour	Mild	14(56)	16(64)	1.61	0.448
	Moderate	11(44)	8(32)		
	Severe	0(0)	1(4)		
NRS at 4 hours	Mild	23(92)	13(52)	9.92	0.002
	Moderate	2(8)	12(48)		
	Severe	0(0)	0(0)		
NRS at 8 hours	Mild	20(80)	19(76)	0.11	0.733
	Moderate	5(20)	6(24)		
	Severe	0(0)	0(0)		
NRS at 24 hours	Mild	25(100)	25(100)	-	-
	Moderate	0(0)	0(0)		
	Severe	0(0)	0(0)		

4.15 Postoperative Systolic Blood Pressure

The postoperative systolic blood pressure for the intervention group remained stable from the first hour to the 8th hour then declined slightly till the 24th hour. That of the control group rose from the first to 4th hour then sharply came down till the 24th hour. The F-test conducted at the different time points did not show any statistically significant difference between the two groups (*F-test* =0.33; *p value* =0.569)

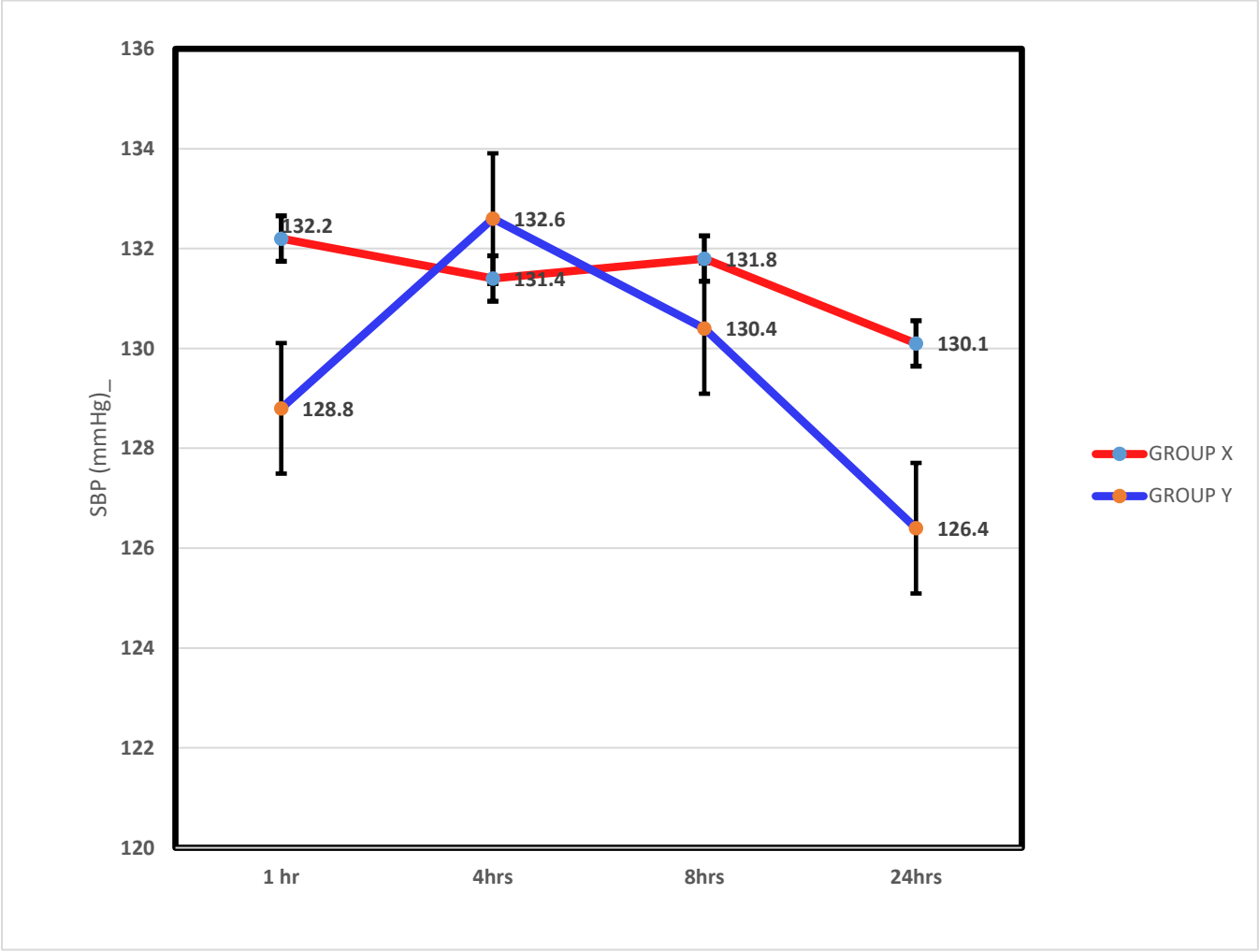

Figure 4.19: Time series plots of postoperative systolic blood pressure

The mean postoperative systolic blood pressure of the intervention group was slightly higher than that of the control group however the difference between the two groups was not statistically significant as shown in figure 4.20 (F-test = 0.33: *p-value* =0.569)

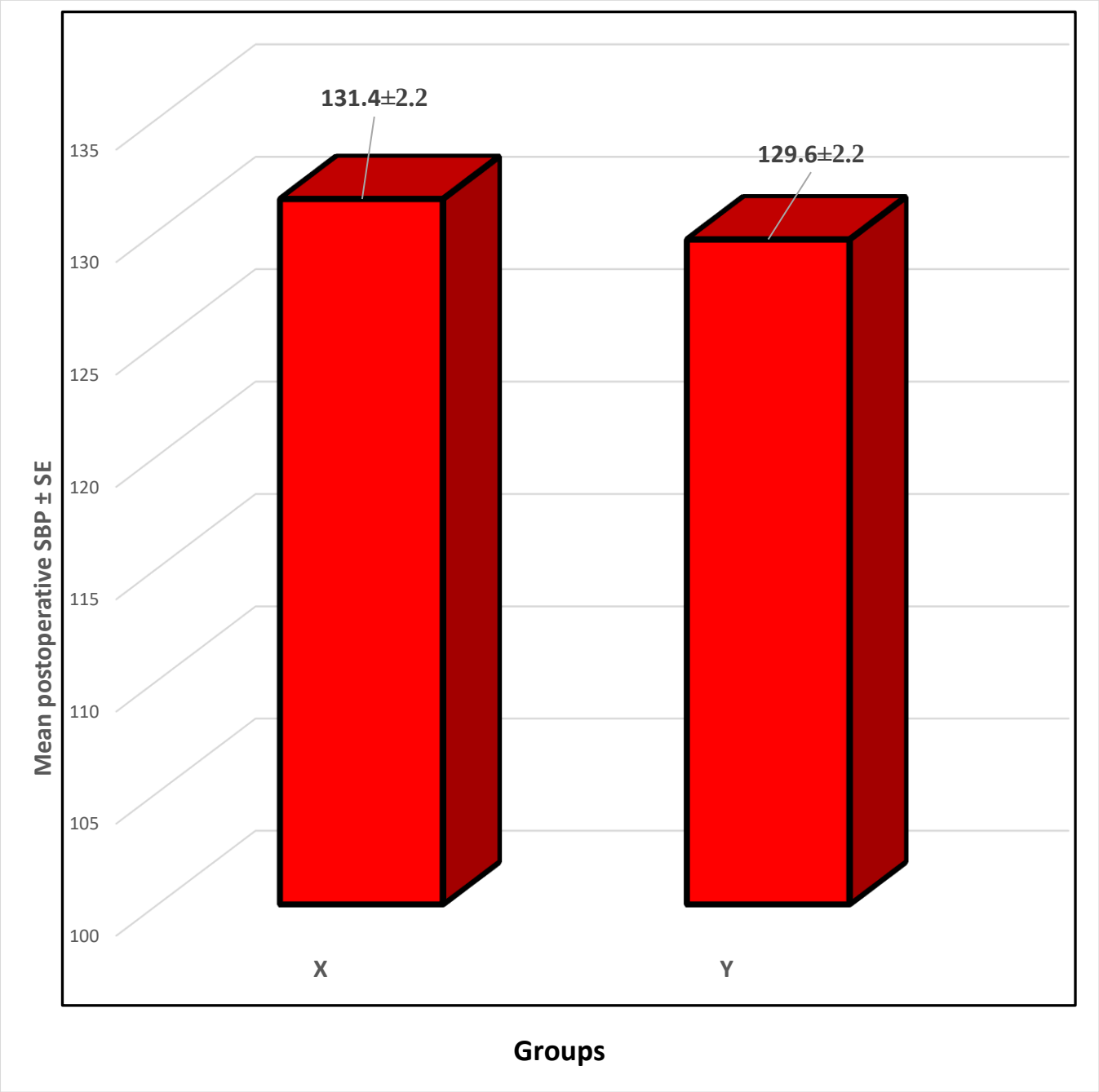

Figure 4.20: Post-op Mean SBP between the two groups

4.16 Postoperative Diastolic Blood Pressure

The mean postoperative diastolic BP in the intervention group reduced slightly and then plateaued whereas that in the control group increased slightly initially and also plateaued. Within the first 24 hours postoperative time, the variations in the mean diastolic blood pressure was not statistically significant between the two groups at each measured time point (*F-test* =0.610: *p-value* = 0.438).

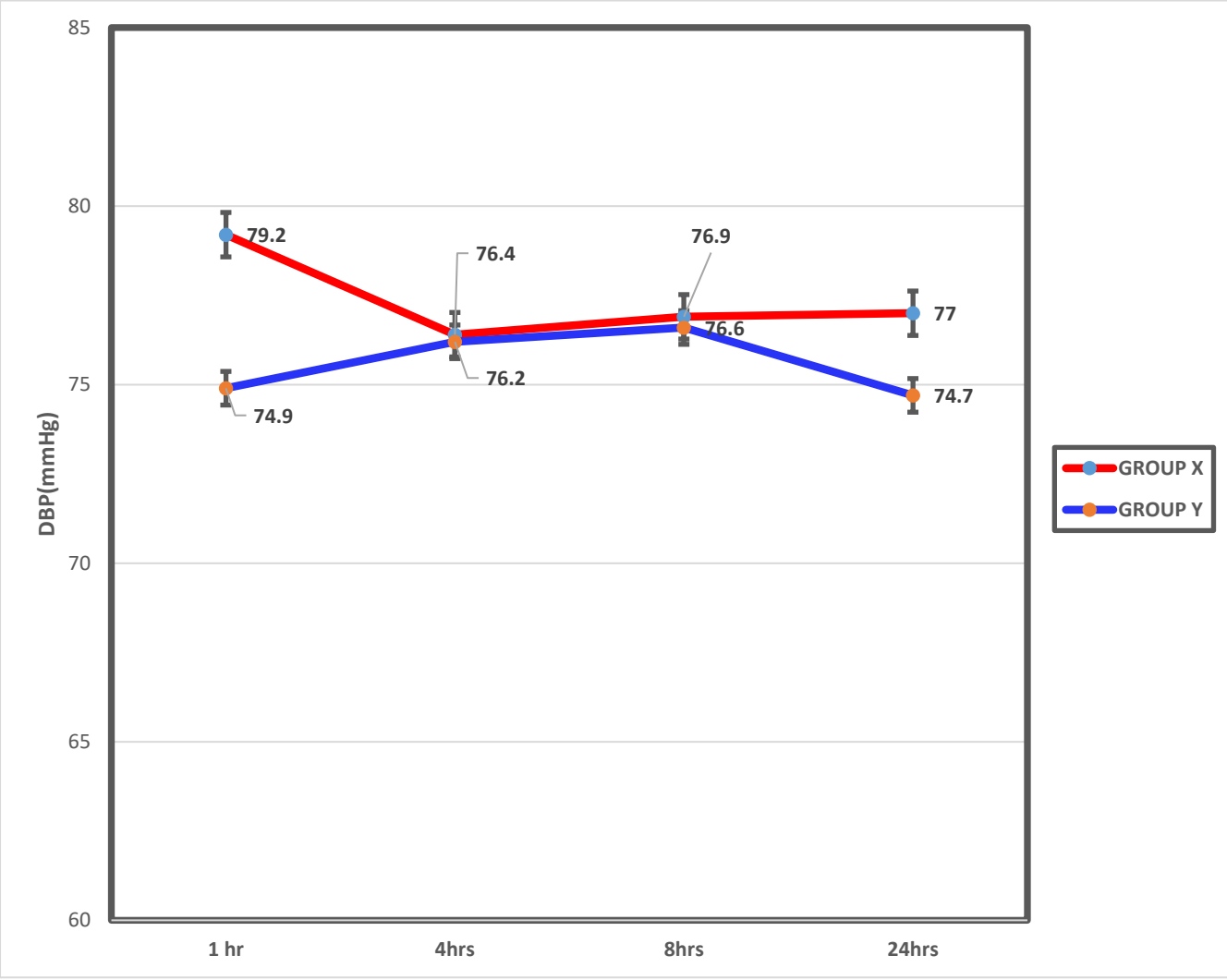

Figure 4.21: Time series plots of postoperative diastolic blood pressure

Figure 4.22 shows that the postoperative mean DBP for the intervention group was higher than the control group. However, the difference was not statistically significant (F-test = 0.61: p-value = 0.438)

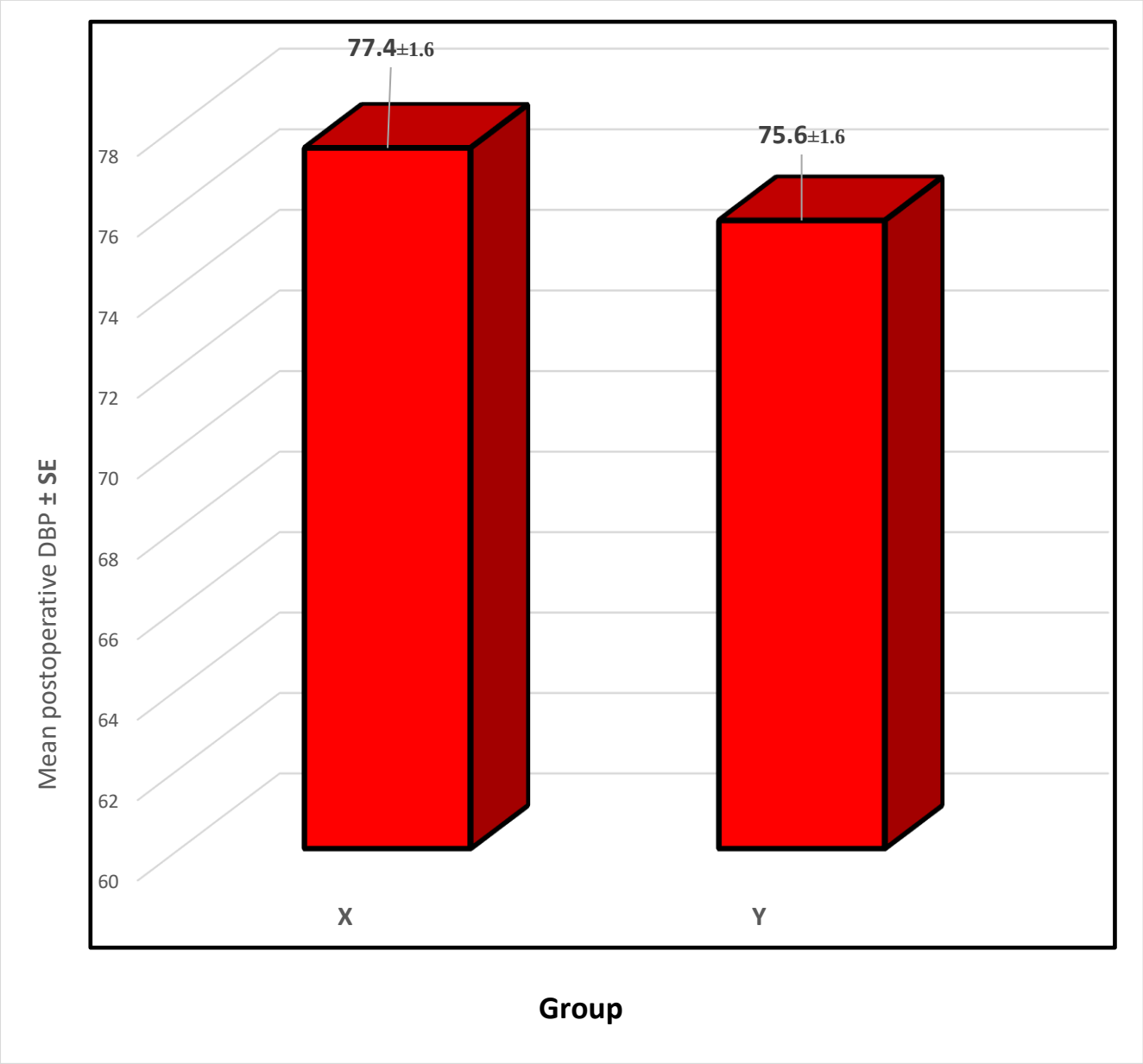

Figure 4.22: Post-operative mean DBP between the groups

4.17 Postoperative Mean Arterial Pressure

The mean arterial pressure in the intervention group was high in the first hour(100mmHg) then dropped to 94.3mmHg in the fourth hour and plateaued afterwards. The MAP of the control group was initially lower than that of the intervention group with a value of 94.8mmHg then remained steady for the first 24 hours. Although the MAP of the intervention group was lower than that of the control group after the 4th hour, the difference was not statistically significant at the various time points (F-test =0.13; *p-value* = 0.720)

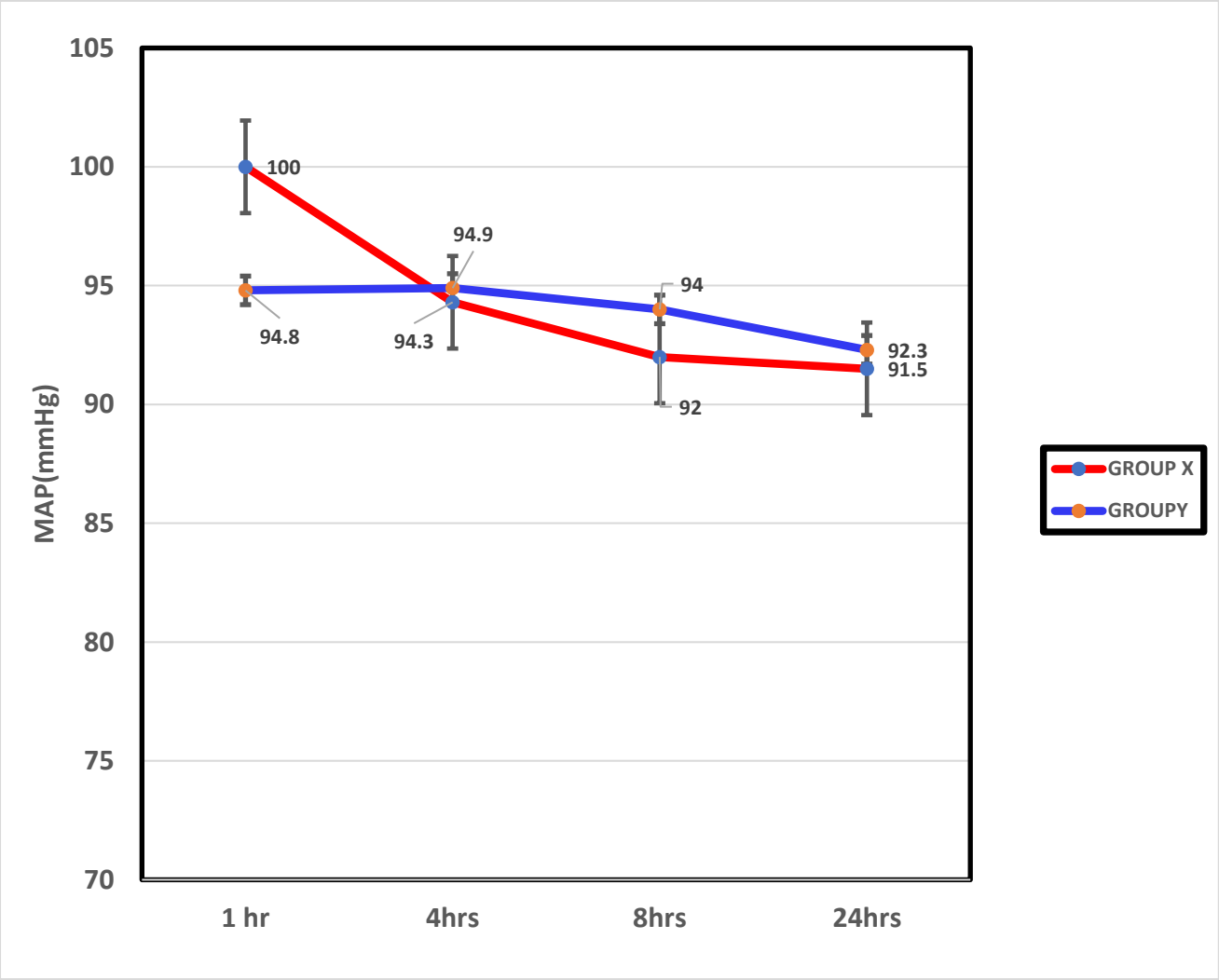

Figure 4.23: Time series plot of postoperative mean arterial pressure

The mean postoperative mean MAP was comparatively the same between the two study groups with no statistically significance difference between them as shown in Figure 4.24 (F-test =0.13: *p-value* = 0.720).

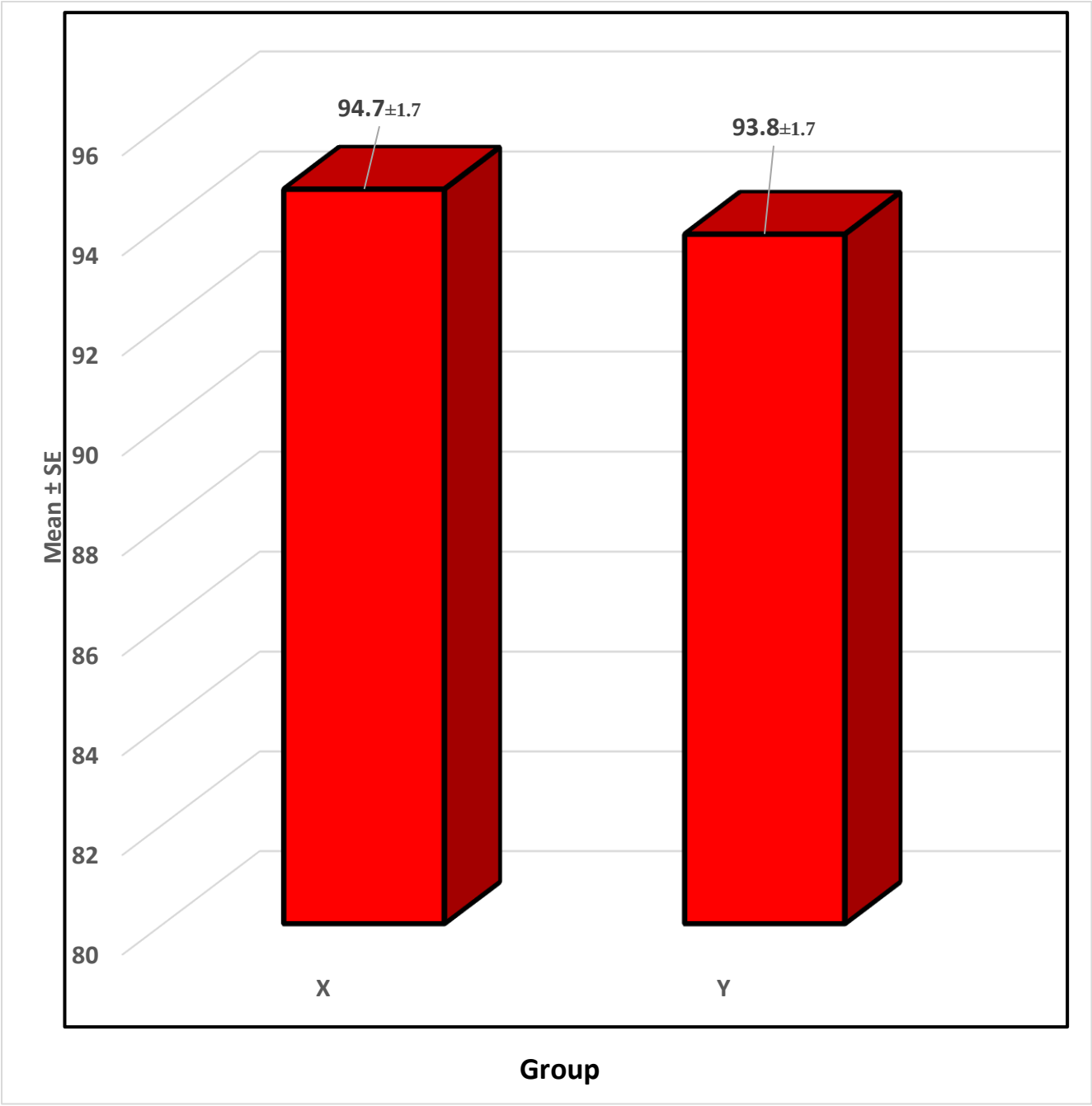

Figure 4.24: Postoperative mean MAP between the groups

4.18 Postoperative Heart Rate

The mean heart rate in the intervention group initially dropped from 83bpm in the first hour to 79.5bpm in the fourth hour. Whereas that of the control group rose from 79bpm to 81.4bpm. Thereafter, there was a general decline in heart rate in both groups but the control group had a greater drop than the intervention. However, a F-test conducted did not show a significant difference between the two group at the various time points (F-test =0.25; *p-value*=0.617).

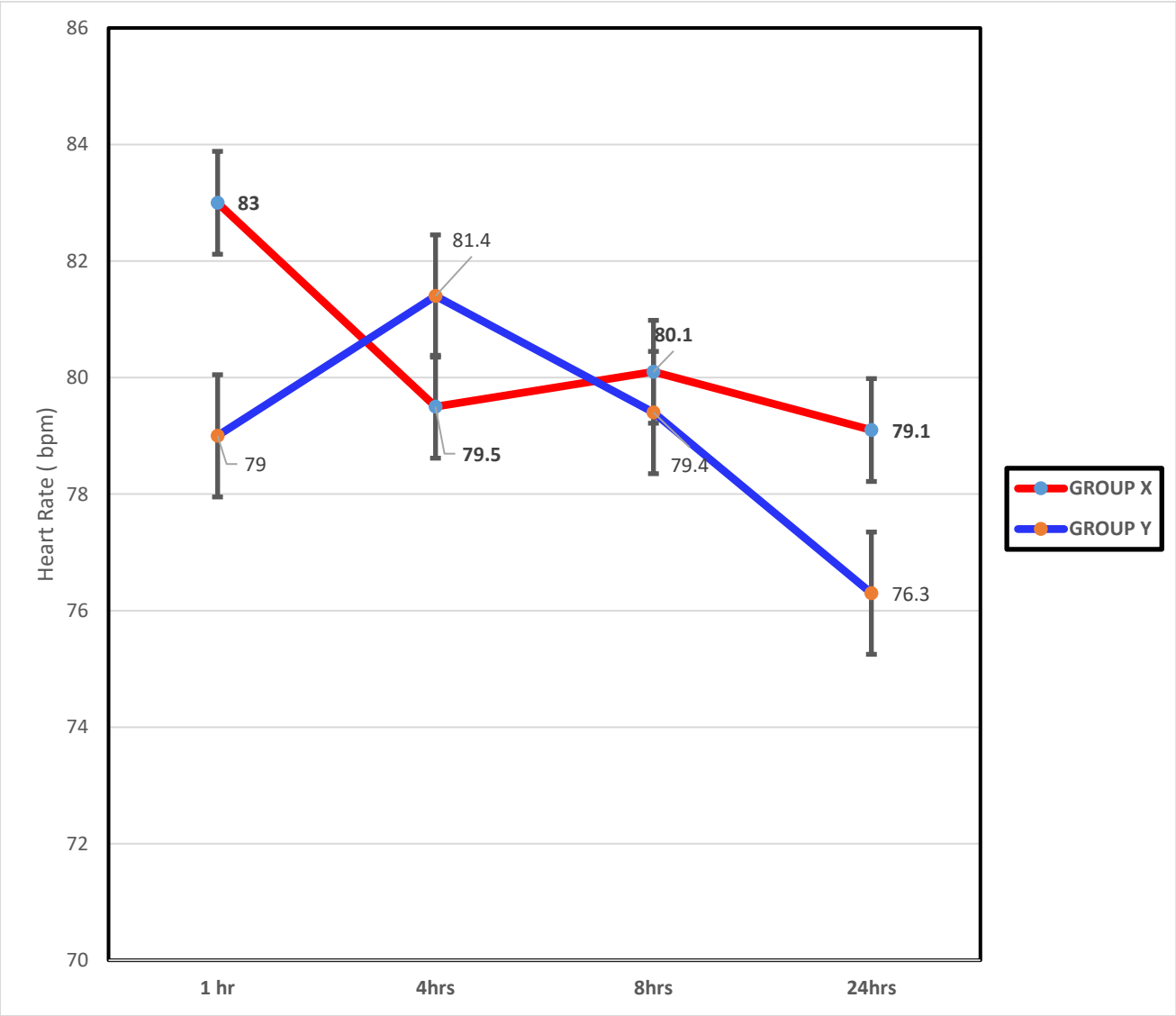

Figure 4.25: Time series plot of postoperative heart rate

Figure 4.26 shows the postoperative mean heart rate between the two study groups. An F-test done showed there was no statistically significant difference (F-test = 0.13: *p-value* = 0.720)

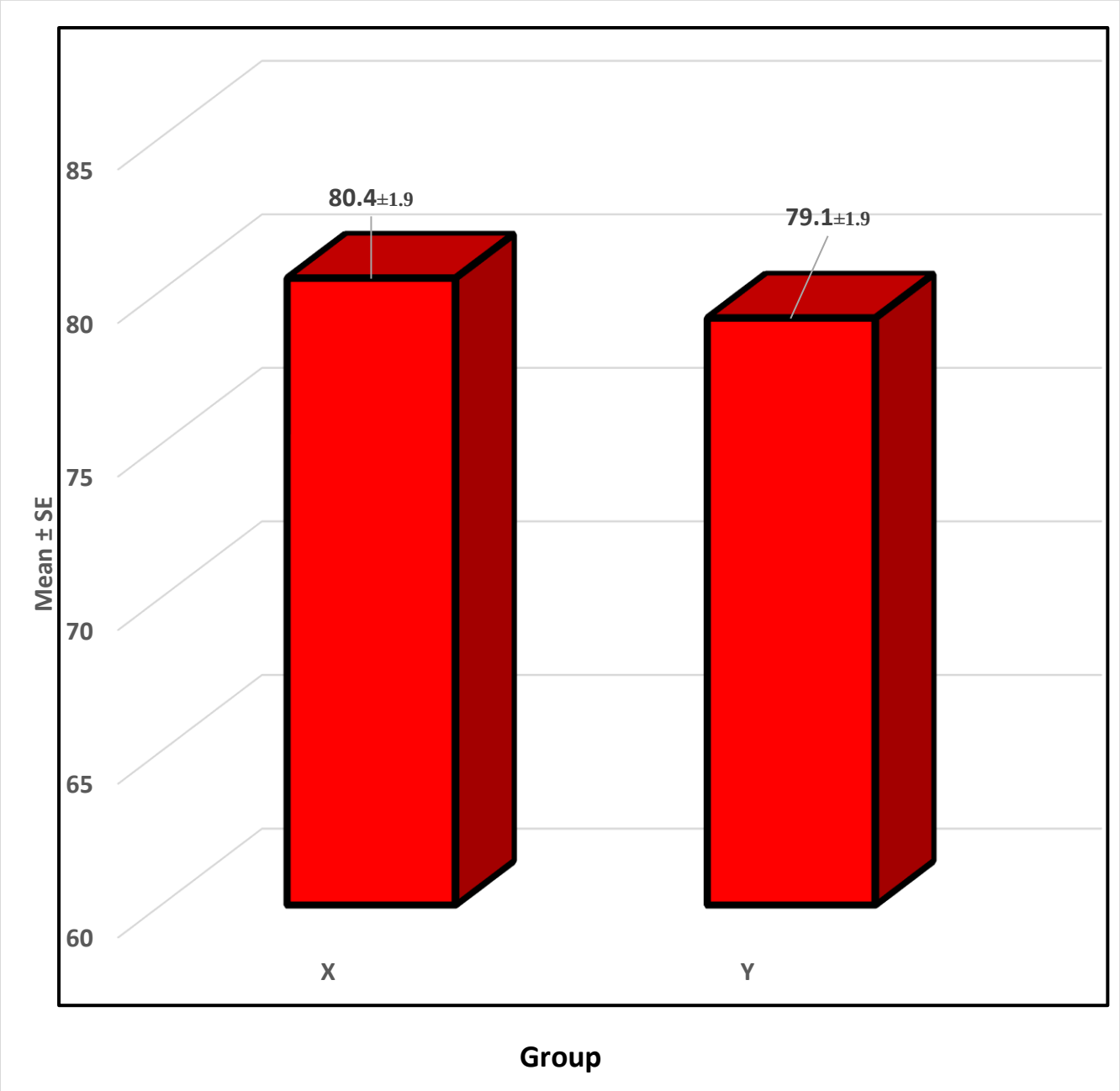

Figure 4.26: Postoperative mean Heart rate between the groups

4.19 Postoperative Respiratory Rate

In the postoperative period, respiratory rate in both groups initially went up and then came down steadily after the fourth hour. Respiratory rate in the intervention group was slightly higher than that in the control group. A F-test conducted did not show any statistically significant difference between the two groups at the various time points (F-test =3.14: *p value* =0.083)

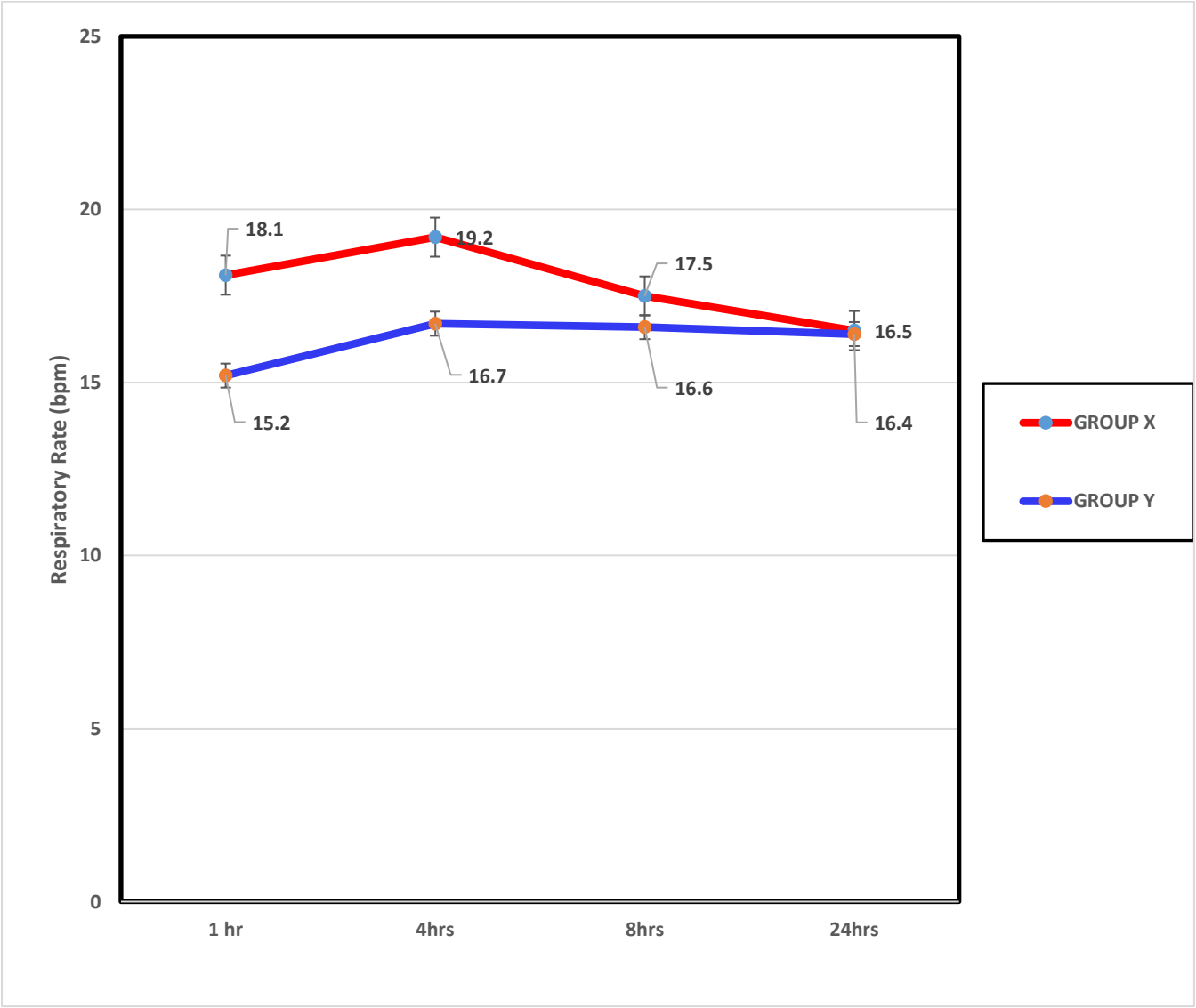

Figure 4.27: Time series plot of postoperative respiratory rate

Figure 4.28 shows the postoperative mean respiratory rate between the two study groups. Although the postoperative mean respiratory rate for the intervention group was comparatively higher than the control group, the difference was not statistically significant (F-test =3.14: *p-value*= 0.083).

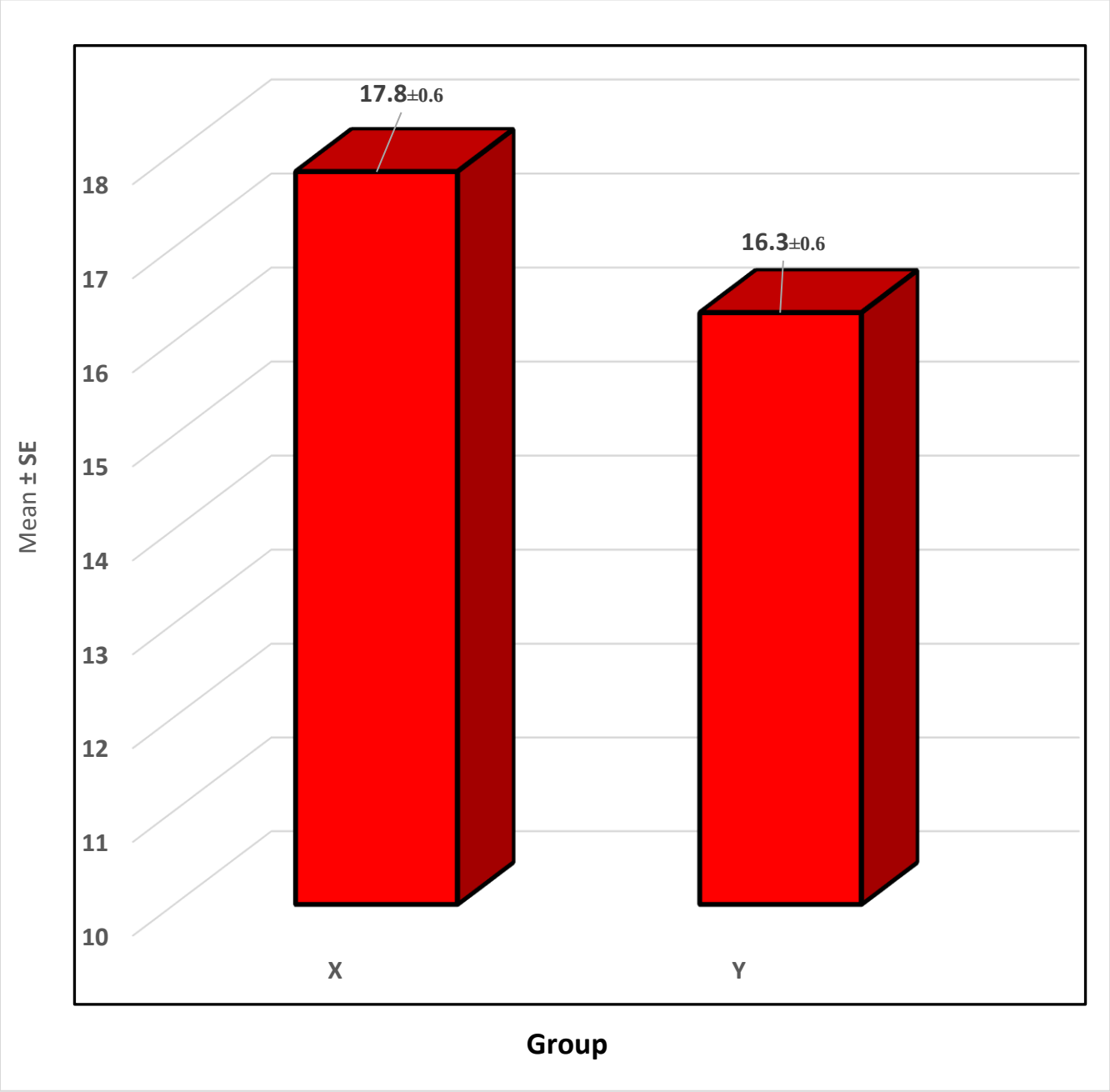

Figure 4.28: Postoperative mean respiratory rate between the groups

4.20 Total Opioids Consumed

In this study, the mean total opioids consumed (morphine equivalent) by study participants intraoperatively was highly significant (11.6±1.5mg) compared to that consumed postoperatively (7.7±6.5mg) as shown in Figure 4.29 below (t-test=4.44; p<0.0001).

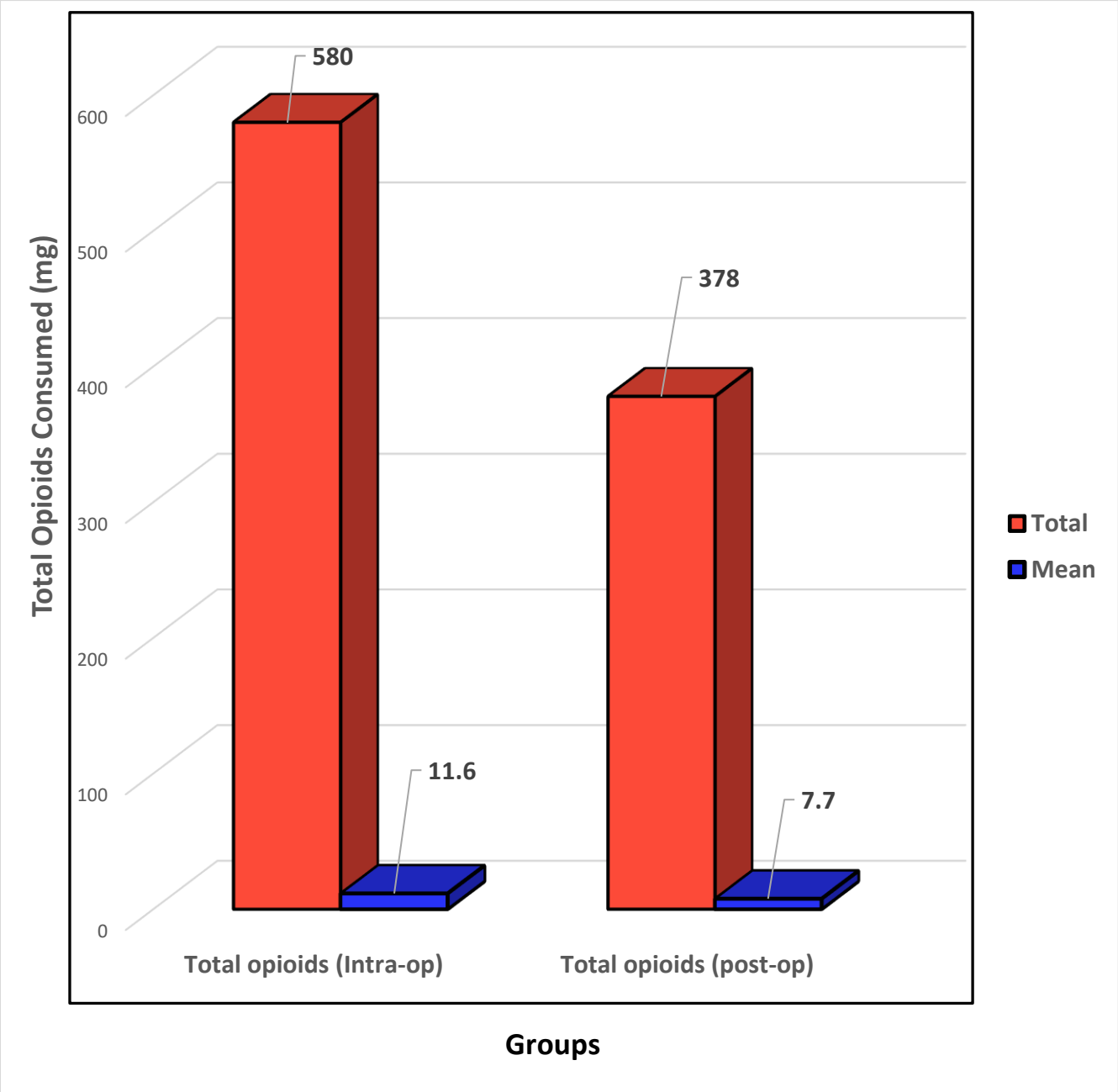

Figure 4.29: Intraoperative and postoperative opioid consumption: Intraoperative and postoperative opioid consumption

4.21 Intraoperative Opioids Consumed for Groups

The mean intraoperative opioid consumed (morphine equivalent) was slightly higher in the control group (11.9±1.5mg) than it was in the intervention group(11.3±1.5mg), however the difference was not statistically significant (t-test=1.51; *p value* = 0.131)

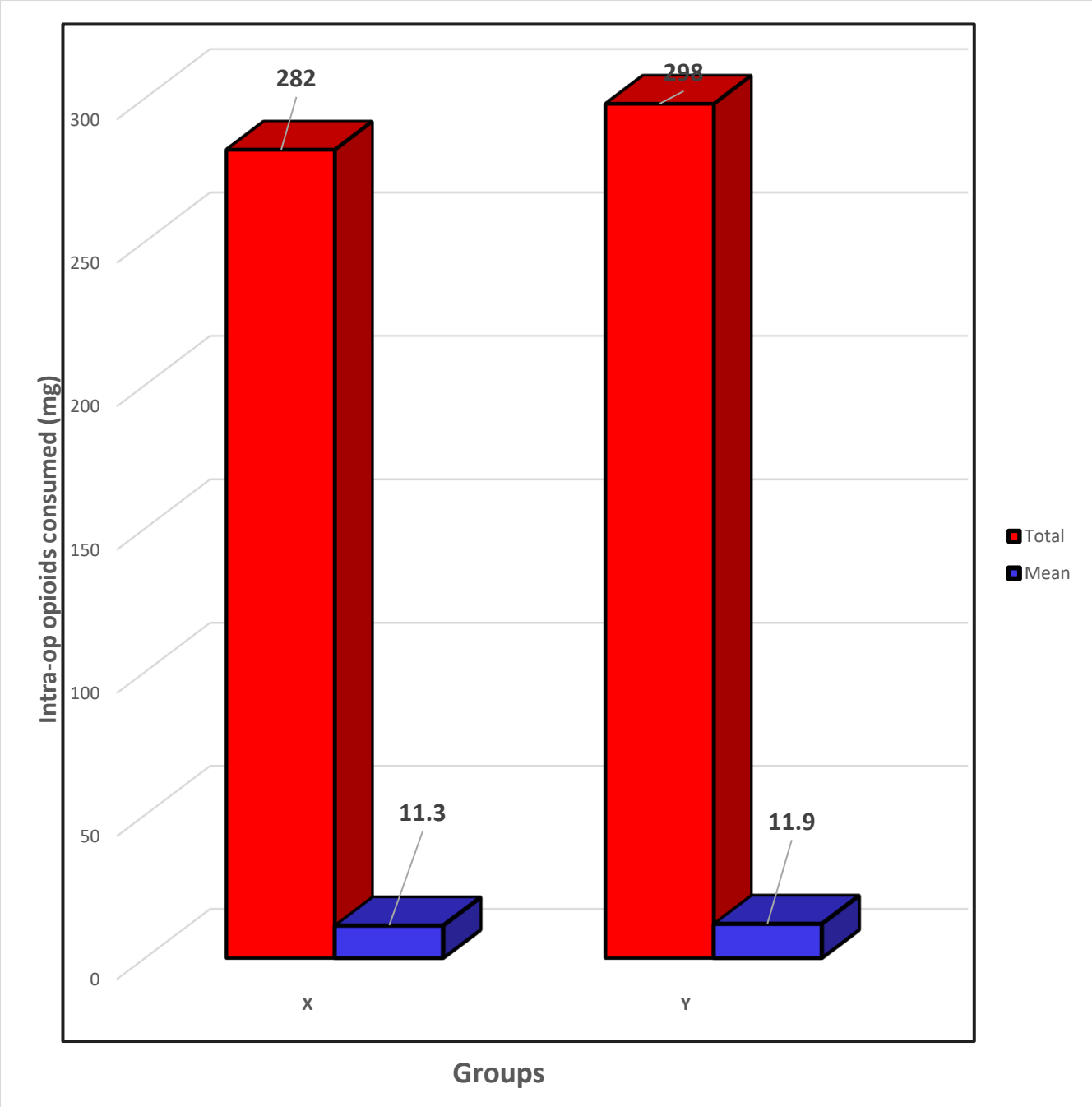

Figure 4.30: Comparison of intraoperative opioids consumed between the groups

4.22 Postoperative Opioids Consumed Between the Groups

The total opioids (morphine equivalent) consumed postoperatively in the control group was 263mg which is about twice as high as that in the intervention group which is 115mg. There was statistically significant difference in the postoperative opioid consumption when comparing the intervention group to the control group (4.6±5.7mg versus 10.5 ± 6mg) respectively (t-test=3.56; *p value* of 0.001).

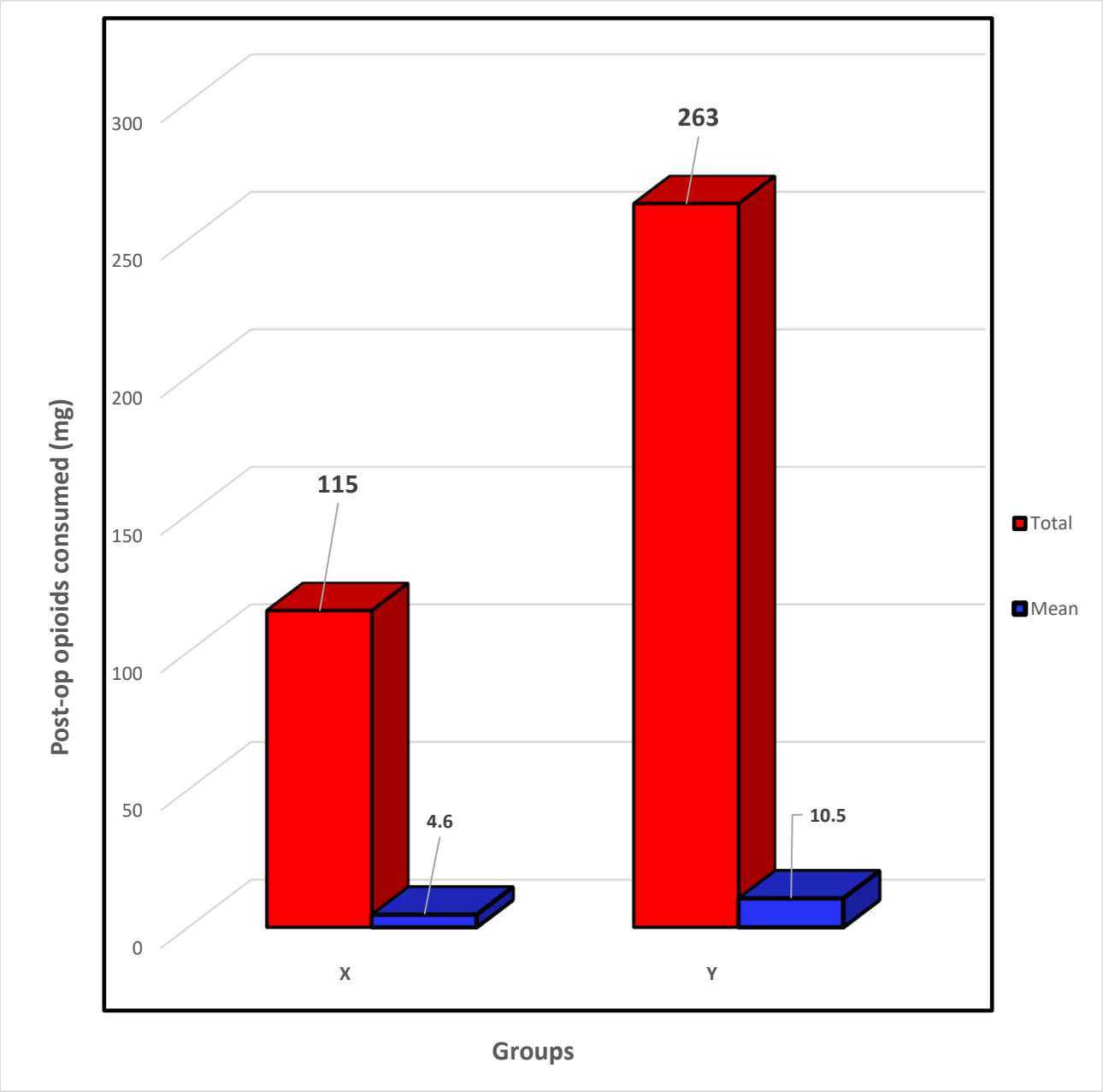

Figure 4.31: Comparison of postoperative opioids consumed between the groups

4.23 Incidence of PONV

Most participants in this study did not experience PONV, however the highest incidence of mild PONV occurred at the 4-hour period. One patient in the control group had moderate PONV 8 hours postoperative time. Between the groups the incidence of PONV was not statistically significant as shown in the Table 4.9 below.

Table 4.9: Incidence of PONV between the Groups

Observation Time Point	**PONV Severity**	**Groups: n(%)**		**Fisher's exact test**	***p-value***
		Intervention	**Control**		
1hr	**None**	24(96.0)	23(92.0)	0.36	1.000
	Mild	1(4.0)	2(8.0)		
4hrs	**None**	24(96.0)	19(76.0)	4.15	0.098
	Mild	1(4.0)	6(24.0)		
8hrs	**None**	24(96.0)	21(84.0)	2.21	0.349
	Mild	1(4.0)	3(12.0)		
	Moderate	0(0.0)	1(4.0)		

4.24 Patient Satisfaction Between the Groups

Generally, patients in both groups were very satisfied with their postoperative pain management. A slightly higher number of patients in the intervention group were somewhat satisfied than in the control group. However, there was no statically significant difference in the level of satisfaction in the two groups as shown in Table 4.10 below (*p-value* 1.000)

Table 4.10: Patient satisfaction between the groups

Satisfaction level	**Groups: n (%)**		**Fisher's exact test**	***p-value***
	Intervention	**Control**		
Very Satisfied	19(76.0)	19(76.0)	1.07	1.000
Somewhat satisfied	6(24.0)	5(20.0)		
Neutral	0(0.0)	1(4.0)		

CHAPTER 5: DISCUSSION

5.1 Characteristics of Study Groups

The study groups were comparable in terms of age, weight, height, and Body Mass Index. Baseline haemodynamic variables were comparable in the two study groups.

The mean age of patients in this study was 47.02±13.67 years. This finding is similar to the study by Brakohiapa et al.[186] in Ghana where the mean age of patients with breast cancer was found to be 48.7±10 years. Previous reports predicts 40 years as the peak age of breast cancer in Sub-Saharan Africa.[187–190] A study by Fregene et al.[187] revealed that the median age at which breast cancer is diagnosed amongst Caucasian-American women is 63 years. African-American women in the same environment have a median age at diagnosis of 57 years. The difference in age at diagnosis between Caucasian and people of African descent has been attributed to genetic factors. This unfortunate finding has economic impact on developing countries since breast cancer affects mainly people in their productive years. The consequence of this is the loss of valuable man-power and reduced productivity at work. Most importantly, the death of these women results in a lot of children becoming orphans. Since majority of women in Ghana who suffer from breast cancer are premenopausal, awareness campaigns should target these group of people. Breast screening should also be started early.

In this study the mean BMI of the patients was 28 kg/m2 which falls within the overweight category.[191] There have been multiple studies showing a strong association between high body mass index and higher risk of breast cancer.[192–195] Women who are obese are at a higher risk of all-cause and breast cancer specific mortality when compared to non-obese women with breast cancer.[196] People of Asian heritage, have a substantially stronger link between increasing BMI and increased breast cancer incidence than people from Europe, North America, and Australia. [61] There is increased aromatization of adipose tissue leading to high levels of oestrogen in the obese women. More so there is an overexpression of pro-inflammatory cytokines, insulin resistance, increased activation of insulin-like growth factors, adipocyte-derived adipokines, hypercholesterolemia and excessive oxidative stress. All these factors contribute immensely to the development of breast cancer in the obese.[197] Tumour formation and aggressiveness is also exacerbated by high plasma cholesterol levels in the obese.[198] There is a rise in BMI in the Ghanaian population as evidenced by a meta-analysis by Ofori-Asenso et al.[199] estimating the prevalence of overweight and obesity in Ghana to be 17% and 25%. In

our study most of the patients were overweight which is a slight deviation from a study conducted by deGraft-Johnson et al.[200] which showed most patients with breast cancer in Ghana were obese. The possible reason for this could be the fact that as part of my exclusion criteria, women with BMI greater than 35 were excluded, in order to eliminate the risk of local anaesthetic toxicity.

5.2 Indication for Breast Surgery

The main indication for breast surgery in this study was breast cancer. Forty-three (22 intervention case and 21 controls cases) patients representing 86% of the subjects had breast cancer. There was no statistically significant difference (*p value* =0.855) between the number of patients with breast cancer in the control group compared to those in the intervention group. One of the major indications for breast surgery in Sub-Saharan Africa is breast cancer. Patients often present late with advanced disease so other modalities of management cannot be explored.[5] The main causes of delay are patients' lack of understanding of the seriousness of their disease and their desire to seek treatment from alternative healers before seeking medical help.[201] Patients frequently stated that they were unaware of the consequences of their sickness or that they believed it would go away without therapy.[202] deGraft-Johnson et al.[200] also reported that 89% of patients coming for breast surgery in the Korle bu Teaching Hospital was as a result of breast cancer which is similar to the findings in this study. The Korle Bu teaching hospital being the largest referral centre in Ghana serves the entire country and some patients in the west African subregion. The high incidence of breast cancer surgery at the study site corroborates a study by Brakohiapa et al.[186] that in a ten year period the incidence of breast cancer at the study site increased from 13% to 15%.

5.3 Types of Surgery

This study revealed that modified radical mastectomy is the most performed breast surgery at the study site with an incidence rate of approximately 60%. This finding is in keeping with findings by Sutter et al.[202] that surgery is the primary form of treatment of breast cancer in Africa. The rates of surgical treatment vary across the different countries in Africa ranging from 35.2% in Nigeria to 100% in Cameroon.[202] When surgical options are considered, the most common surgery is a mastectomy. All institutions surveyed across the continent perform mastectomies at a rate well over 50% and sometimes exceeding 90%.[203–206]Modified radical

mastectomy is most frequently performed, which consists of removing the whole breast tissue along with the axillary tail and complete clearance of axillary lymph nodes and connective tissue.[207,208]

The reasons attributed to this is that, treatment is often not readily available, delayed or prohibitively expensive therefore patients usually present late with advanced disease. Another factor that was noted in an article by Kantelhardt et al.[209] is that screening via mammography and the appropriate resources for proper follow-up of any results are not widely available in Africa.

Breast conserving surgeries and lumpectomies are still uncommon in the sub-region, because most patients report to the hospital with advanced stages(III and IV) of invasive cancer.[204,210] Therefore the option for conservative surgery in the absence of neoadjuvant chemotherapy is limited. More so, assessing surgical margins for tumour-free tissue is usually impossible, and postoperative follow-up is infrequent.[208,211] In contrast, in developed countries, most breast cancer operations are breast conserving surgeries.

5.4 Neoadjuvant Chemotherapy

In this study, 64% of patients received neoadjuvant chemotherapy before coming for their surgery. There is a huge disparity in chemotherapy rates across the African continent. The percentage of patients receiving neoadjuvant chemotherapy in hospitals in Ghana, South Africa, Nigeria, Cameroon and Rwanda ranges from 28% to 85% as reported by Sutter et al.[202] The percentage of people receiving chemotherapy in this study is twice as high as that recorded by deGraft-Johnson et al.[200] in their study three years ago at the same study site. Possible explanation for this difference could be the fact that most of the patients in this present study were reporting late with advanced disease for treatment due to the covid-19 pandemic. Therefore, the patients were presenting with advanced disease that needed to be downstaged with neoadjuvant chemotherapy before proceeding with surgery. Another explanation offered by the surgical team for a possible increase in neoadjuvant chemotherapy is that, giving the patient neoadjuvant chemotherapy helps to determine if the tumour will respond to adjuvant chemotherapy postoperatively. If the tumour does not shrink in size with neoadjuvant chemotherapy, then it is unlikely to respond to the same medications when given postoperatively. This information helps them to determine which chemotherapy agent to use postoperatively.

5.5 Intraoperative Hemodynamic Parameters

In general, the intraoperative systolic blood pressure, diastolic blood pressure, mean arterial blood pressure in both study arms declined intraoperatively with time. Although the hemodynamic variables were low in both groups, the intervention group had lower values than that of the control group, the difference between them was not statistically significant (p value <0.05). These findings agree with that of the study of Lee et al.[212] in which ultrasound-guided serratus anterior plane block was performed for patients coming for video-assisted thoracoscopic lobectomy. They also noted that, there were no significant differences in systolic blood pressure and heart rate (HR) between the intervention group and the control group at each time point, although the values of the intervention group were lower. These difference could be attributed to the fact that SAPB blocks peripheral nerves, that is, the lateral cutaneous branches of the intercostal nerves.[13] Since nociceptive afferent transmission is blocked, the sympathetic response of increasing blood pressure and heart rate is reduced.[212] Perhaps the study was not powered to detect the differences in the hemodynamic variables.

5.6 Intraoperative Opioid Consumption

In this study, our finding of no significant difference in the mean intraoperative opioid consumption of the intervention and control groups is no different from what was reported by Nian-Qiang Hu et al.[168] in their systematic review and metanalysis to assess the safety and efficacy of SAPB for postoperative analgesia after breast surgery. A total of 13 studies comprising 826 patients were analysed. There was negligible difference observed in the intraoperative opioid consumption between intervention group and control group (mean difference, −9.85 mg of oral morphine equivalent; 95% CI, −19.52 to −0.18; ; $I^2 = 94\%$) This finding may be because the extent of SAPB was not sufficient to control intraoperative pain. The blocks are performed after the patients are anaesthetised, therefore there is no opportunity to actually test if the block is working or not and the extent of the block. Another possible explanation is that the deep serratus anterior plane block results in inconsistent block. A study by Mayes et al.[213] to determine the spread of injectate and investigate the anatomical basis of the serratus anterior plane block reported that when methylene blue is injected deep to the serratus anterior muscle, the spread is not always homogenous. Results similar to this study were reported by Alessandro et al.[156] in patients undergoing thoracoscopic surgery.

In a similar study, Kunigo *et al.*[214] performed ultrasound-guided SAPB on nine adult female patients scheduled for modified radical mastectomy to determine the dermatomal spread and analgesic effect of serratus anterior plane block. The patients were randomly assigned to receive 20 or 40 mL of 0.375% ropivacaine. The primary end point was the number of affected dermatomes as assessed by cold test and pinprick test 20 minutes after the block procedure. The number of affected dermatomes assessed by the cold test for patients receiving 40 mL of 0.375% ropivacaine was significantly larger than that for patients receiving 20 mL (P = 0.002; 6 [5–7] vs 4 [3–4] dermatomes). Similarly, with the pinprick test, the affected area was larger for the 40 mL group than for the 20 mL group (P = 0.009; 4 [2–6] vs 2[1–3] dermatomes). This study revealed that significantly wider dermatomes were anesthetized after serratus plane block with 40ml of 0.375% ropivacaine than with 20 ml of the same solution. In their landmark study, Blanco et al. reported that serratus plane block with 0.4 ml/kg of 0.125% levobupivacaine affected T2–T6 at the minimum and to T2–T9 at the maximum.

Interestingly, the affected dermatomes in the 40ml group in Kunigo et al.[214] study was not as wide as suggested by Blanco et al.[13] study. This difference might be due to point of entry of the peripheral nerve needle. Whereas the tip of the needle in former's study was over the fourth rib, that of the latter was over the fifth rib. This could account for the difference in spread of the injectate.

The best technique for consistent successful block after serratus plane block has not been extensively studied. Biswas et al.[146] evaluated the impact of volume, level and site of injection on the extent of injectate spread and how these factors influence anaesthetic coverage.

They performed ultrasound-guided methylene blue dye injection in the hemithoraces of 39 cadavers. Dye injection were performed in four different ways: one 20ml bolus, either superficial or deep to the serratus anterior muscle, at the fifth rib level, or 40ml bolus either superior or deep or deep to the SAM, one at the third rib and one at the fifth rib level. After 20 minutes of the injection, the chest walls were dissected. The hemithorax that had 40ml methylene blue injection had T2-T5 intercostal nerves completely stained, while only the T3-T5 nerves were completely stained in the side with 20ml methylene blue injection. The study revealed that the extent of dye spread was mostly influenced by the volume of injection rather than the plane of injection (superficial vs deep to SAM).

In contrast, a randomised trial to evaluate the effect of pre-operative serratus anterior plane block on postoperative pain and opioid consumption after thoracoscopic surgery revealed that serratus anterior plane block reduced mean (SD) remifentanil dose during surgery, compared to those who did not receive a block(0.12 (0.06) $mg.h^{-1}$ vs. 0.16 (0.06) $mg.h^{-1}$, p = 0.016).[215]

5.7 Post-Operative Pain Intensity

Pain is one of the major complaints after breast surgery, therefore accurate evaluation of pain is fundamental to giving a timely and appropriate treatment to patients. Numerical Rating Scales (NRS) have shown high correlations with other pain-assessment tools in several studies.[110] The feasibility of its use and good compliance have also been proven.[112] In this study the NRS was chosen because it is easy to administer it verbally. However, unlike the VAS/GRS, it cannot necessarily be treated as ratio data.[113]

In this study, the NRS for both study groups declined over time but there was a statistically significant difference between the intervention group and the control group. At the various time points, the most statistically significant difference in NRS score between the study groups was recorded at the 4-hour postoperative time.

The NRS recorded at 4 hours postoperative time showed mild pain in 92% of the intervention group compared to 52% in the control group. More participants in the control group, 48%, had moderate pain compared to 8% in the intervention group. This observation could be explained by the fact that morphine has a 3-4 hour duration of action, therefore any intraoperative opioid administered to the control group would have worn off by the fourth hour, causing them to experience pain.[216] Those in the intervention group, on the other hand, benefited from the block.

In a recent RCT by Bhan et al.[217] to assess the analgesic efficacy of serratus anterior plane block in patients having modified radical mastectomy, SAP block was shown to significantly reduce post-operative NRS scores for pain. Post-operative pain scores were significantly reduced at rest and on movement till 6 hours post-operatively. In contrast to our study, they did not give a sham block due to ethical concerns, while in our study, physiological saline was given to the control group. Also, in their study, the patients were not blinded and the blocks were administered before general anaesthesia therefore the risk of assessment bias is possible. The findings of this study are in line with those of previous studies that have shown a reduction in intra-operative opioid requirements and post-operative VAS scores after SAP block.[154,218]

5.8 Postoperative Opioids Consumed Between the Groups

The total opioids (intravenous morphine equivalent) consumed postoperatively in the control group was 263mg which is about twice as high as that in the intervention group which is 115mg. There was statistically significant difference in the mean postoperative opioid consumption in the intervention group and the control group.

This study's finding correlates with a systematic review and meta-analysis by Nian-Qiang Hu et al.[219] which revealed that ultrasound-guided SAPB remarkably decreased the levels of postoperative opioid consumption and decreased pain compared with that in the control group, which indicated that SAPB could provide effective analgesia after breast surgery. However, a recent randomized control trial Abdallah et al.[154] showed that SAPB did not improve analgesic outcomes in patients who underwent ambulatory breast cancer surgery. A possible explanation for this deviation could be the fact that the serratus anterior plane block performed was not extensive enough to provide adequate control of the pain. Also, the sample size of 40 in their study was probably not powered enough to capture the differences in postoperative pain between the intervention and control groups.

5.9 Effect of SAPB on PONV

Postoperative nausea and vomiting is one of the most common complications after general anaesthesia causing significant dissatisfaction amongst patients. It has a reported incidence of over 30% in all postsurgical patients and about 80% in high risk patients.[220] Amongst the predisposing factors, the strongest risk factor is female gender with an odds ratio (OR) of 3, which indicates that female patients averagely are three times more likely than men to suffer from PONV.[220] According to literature, 60% to 80% of patients undergoing breast surgery under general anaesthesia experience PONV.[221] Traditionally, antiemetics have been the main stay of management. However, pharmacological management of PONV is not without adverse effects. A number of research conducted have shown that effective regional anaesthesia can reduce the incidence of PONV by reducing the amount of opioid used perioperatively.[220] In a case report by Tao et al.[222] serratus anterior plane block was used to reduce the incidence of PONV in a high risk patient that had partial hepatectomy for a hepatic tumour. A deep SAPB was performed at T6 and T& level respectively and a catheter left in-situ at the T7 level. It is reported that the patient had excellent analgesia for 48 hours postoperatively and required only

10mg of morphine on first postoperative day. No nausea and vomiting event occurred postoperatively. Unfortunately, this case report involved only one patient.

In their systematic review and meta-analysis of 13 randomised controlled trials, Hu et al.[219] reported that SAPB reduced postoperative nausea and vomiting significantly in 8 trials. In this current study, PONV was generally low amongst the two study groups, however the intervention group had a slightly lower incidence compared to the control group although it was statistically not significant. The highest incidence of PONV in the control group occurred at the four-hour mark postoperatively. This is the period where most of the patients in the control group received opioids for pain control therefore could explain why the incidence of PONV increased. Another reason that could account for the general low incidence of PONV could be as a result of genetic factors. In their study of 800 patients in South Africa, comprising of Africans and non-Africans, Rodseth et al. observed that there was a statistically significant difference in the incidence of PONV between African and non-African groups (27% vs 45%, $P < 0.0001$).The study concluded that non-African ethnicity is an independent predictor of PONV(OR, 2.1; 95% CI, 1.5-2.82).[223]

Effective prevention of PONV is important in the implementation of enhanced recovery after surgery. Reduction of PONV is useful in expediting discharge for patients coming for day surgeries.[224]

5.10 Patient Satisfaction with Post-Operative Analgesia

In this study, participants were asked to rank their satisfaction with analgesia in the first 24 postoperative hours, from ‘very satisfied’ to ‘very dissatisfied.

Generally, patients in both groups were very satisfied with their postoperative pain management although those in the intervention group were more. A slightly higher number of patients in the intervention group were ‘somewhat satisfied’ compared to those in the control group. However, there was no statistically significant difference in the level of satisfaction between the two groups. This finding corroborates the results from a study by Park et al.[225] that demonstrated that patients who had preoperative serratus anterior plane block for VATs were more satisfied with their postoperative analgesia than the control group that did not receive any block. However, in that particular study, they did not control the local anaesthetic block with

placebo injectate or a sham procedure, therefore the risk of performance and assessment bias was high.

5.11 Limitations

Some of the limitations encountered during this study are as follows:

- Obtaining the NRS score for some of the patients from other West African countries was difficult because of language barrier. Although a good attempt was made in explaining the NRS score to them, it is possible they may have over or underestimated their pain scores.
- Accurate assessment of postoperative opioid consumption would have been obtained if patient-controlled analgesia (PCA) equipment were available. This is because some of the ward nurses are sometimes reluctant to give opioids to patients when they request for it because of a perceived fear of the patient becoming dependent on them. Unfortunately, PCA devices are unavailable at the study site.
- The sample size was relatively small and probably a larger sample size may have improved the power of the study.
- There are no existing studies on this subject that the researcher is aware of at the Korle Bu Teaching Hospital or Ghana. Comparison of results was mainly done with studies carried out in the Western countries. There will be differences in socio-demographic characteristics and cultural differences towards the perception of pain.
- This study was a single centre trial; therefore, caution must be exercised in extrapolating the study findings to the general population. Multiple studies will have to be carried out across the country in order to generalize the research findings.
- For those in the intervention group it was difficult to assess if the block actually worked and also to ascertain the extent of dermatomal coverage. This is because the blocks were performed after patients have had general anaesthesia. Perhaps if the blocks were given before induction of anaesthesia, then accurate assessment of all the dermatomes involved would have been known.

CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusion

In patients undergoing breast surgery, serratus anterior plane block results in a reduction of postoperative pain assessed by numerical rating scale (NRS) scores in the first 24-hour postoperative period.

SAP block also results in a clinical but not statistically significant reduction in intraoperative opioid consumption.

However, it results in a significant reduction in postoperative opioid consumption in the first 24-hours postoperatively compared to placebo.

SAP block also decreases clinically the incidence of PONV in patients undergoing breast surgery. However, the reduction is not statistically significant.

Patients who had SAP block were generally more satisfied with their postoperative pain management.

No patient developed complications related to the application of the block.

6.2 Recommendations

The study makes the following recommendations:

- All patients coming for breast surgery who have no contraindications to local anaesthetics should be offered serratus anterior plane block as it is effective in reducing perioperative pain and PONV without any significant adverse effects.

- Every trainee anaesthetist should be encouraged to learn how to perform a serratus anterior plane block because this block is very easy to do and has a very good safety profile.

- Patients with rib fractures who end up in the recovery ward and intensive care unit/high dependency unit should also be offered serratus anterior plane block.

- A larger, multi-centre study is required on this subject to extrapolate the finding of this study to the general population.

- Future studies should aim at giving the SAP block before induction of anaesthesia so that block failure may not confound the results obtained from the study

- Future investigation is required to determine the severity of acute postoperative pain after breast surgery in the Ghanaian population. Anecdotally, it is believed the local population have lower pain scores than what is reported in literature on Caucasian populations. Although our studies corroborated this assertion our sample size is too small to generalize it to the entire population.

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CHAPTER 7: APPENDICES

7.1 APPENDIX 1- DATA COLLECTION SHEET

DATE:	DIAGNOSIS:
NAME:	NEO-ADJUVANT CHEMO:
AGE:	COMOBIDITIES:
SEX:	WARD:
HEIGHT:	RANDOMIZATION GROUP:
WEIGHT:	CODE:
BMI:	SURGERY START TIME:
ASA:	SURGERY END TIME:

INTRA-OP

	TIME	BP	MAP	HR	RR	FENTANYL	MORPHINE	OTHER DRUGS
Pre-induction								
Post-induction								
Post SAPB								
Incision								
30 min post incision								
1 hr post incision								
Intervention1								
Intervention 2								
Intervention 3								
Intervention 4								

Opioids total								

POST-OP

Time to first analgesic request(medication and dose):

VITALS	TIME				
	<1 POST OP	1HR POST-OP	4HRS POST-OP	8HRS POST-OP	24HRS POST-OP
NRS					
BP					
MAP					
HR					
RR					
PONV					

PONV SCORE [0=NONE; 1=MILD; 2=MODERATE; 3=SEVERE]

OPIOIDS CONSUMED POST-OP	POST-OP TIME								TOTAL
	<1HR	1HR	4HRS	8HRS	24HRS	OTHER	OTHER	OTHER	

MORPHINE									
PETHIDIDE									

Patient satisfaction (Tick): [ ] Very satisfied [ ] Somewhat satisfied [ ] Neutral [ ] Somewhat dissatisfied [ ] Very dissatisfied

7.2 APPENDIX 2-CONSENT FORM

PARTICIPANT INFORMATION AND CONSENT FORM

TITLE: Perioperative analgesic Effect of Serratus Anterior Plane block on Breast Surgery. A prospective, randomized, controlled double blind study conducted at the Korle Bu Teaching Hospital, Accra, Ghana.

Principal investigator:
Dr David Kofi Mensah
Department of Anaesthesia, Korle Bu Teaching Hospital
P. O. Box KB 77 Korle Bu
Email: nanakofimensah4@gmail.com
Mobile: 0202536097

Purpose of study

This study aims to establish that serratus anterior plane block for mastectomy can minimize the requirements for systemic opioids in the perioperative period by providing superior pain relief.

I, the principal investigator is conducting this research to see how effective regional nerve blocks can improve pain relief and reduce the use of opioids in treating pain after breast surgery.

You are being asked to volunteer as a participant in this study. This form is designed to provide you with information about this study and to answer any of your questions. After going through this form you may refuse to participate in the study. This will not affect your management in any way.

Procedure

If you decide to participate in the study, a local anaesthetic will be infiltrated into the lateral aspects of the part of your chest being operated on, with the aim of blocking nerves that carry pain sensation to that part of your chest. This should result in the reduction of pain during and after surgery. This procedure will be performed with an ultrasound machine to enable me see exactly where to inject. The procedure will be carried out only when you are unconscious and under general anaesthesia. Your clinical history will be taken and the details recorded in a

questionnaire. After the operation the amount of pain you feel will be assessed and further pain relief administered to ensure that you are comfortable.

Benefits

This study would help assess whether giving local anaesthesia in this manner can reduce pain and perioperative opioid requirement.

Risks

There is a minute risk of damage to nerves and blood vessels. The nerves targeted during these blocks are superficial and hence access to them is relatively easy. Damage to blood vessels would be minor and is extremely rare. There is a minor risk of puncturing your lungs but this risk is reduced by doing the procedure with an ultrasound machine so that the lungs can be avoided. You might experience minor bruising at the site of injection. The procedure will be stopped if you react to the local anaesthetic injection.

Confidentiality

All information obtained on you during the course of the study would be kept confidential. Should the results of the study be published, you will be referred to only as a number.

Participants rights

Your participation in this study is voluntary and you are free to withdraw without penalty at any time. Your surgical management will not be affected. Kindly consent if you are satisfied with this information and will like to participate in this study.

Volunteer agreement

The above document describing the benefits, the risks and procedures for the research title **"Perioperative analgesic effect of serratus anterior plane block on breast surgery"** has been read and explained to me.

I have been given an opportunity to have any questions about the research answered to my satisfaction. I agree to participate as a volunteer.

Name of Participant:……

Signature/Thumbprint of participant:…… Date:……...

Name and signature of person who obtained consent:…….

7.3 APPENDIX 3 – Institutional Review Board Approval Letter

In case of reply the number
And the date of this
Letter should be quoted
My Ref. No. KBTH/IRB/0009/21
Your Ref. No.....

KORLE BU TEACHING HOSPITAL
P. O. BOX KB 77,
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19th October, 2021

DR DAVID KOFI MENSAH
DEPT. OF ANAESTHESIA
KORLE BU

PERIOPERATIVE ANALGESIC EFFECT OF SERRATUS ANTERIOR PLANE BLOCK ON BREAST SURGERY. A PROSPECTIVE, RANDOMIZED, CONTROLLED DOUBLE BLIND STUDY AT THE KORLE BU TEACHING HOSPITAL, ACCRA, GHANA.

KBTH-IRB /0009/2020

Investigator: Dr David Kofi Mensah

The Korle Bu Teaching Hospital Institutional Review Board (KBTH IRB) reviewed and granted approval to the study entitled: "Perioperative Analgesic Effect of Serratus Anterior Plane Block on Breast Surgery. A Prospective, Randomized, Controlled Double Blind Study at the Korle Bu Teaching Hospital, Accra, Ghana"

Please note that the Board requires you to submit a final review report on completion of this study to the KBTH-IRB.

Kindly, note that, any modification/amendment to the approved study protocol without approval from KBTH-IRB renders this certificate invalid.

Please report all serious adverse events related to this study to KBTH-IRB within seven days verbally and fourteen days in writing.

This IRB approval is valid till 30th September, 2022. You are to submit annual report for continuing review.

Sincere regards,

DR. DANIEL ANKRAH
VICE CHAIR (KBTH-IRB)
FOR: CHAIR (KBTH-IRB

Cc: The Chief Executive Officer, KBTH
The Director of Medical Affairs, KBTH

7.4 APPENDIX 4: Butterfly IQ attached to Ipad