

A PROSPECTIVE OBSERVATIONAL STUDY TO
DETERMINE THE USE OF INTRA-OPERATIVE
RESPIRATORY RATE AS AN INDICATOR OF THE
ADEQUACY OF POST-OPERATIVE ANALGESIA – A
PILOT STUDY.

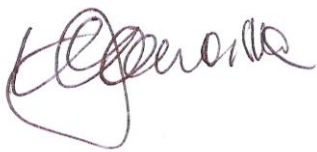
Magdalena Anna Jaworska

A research report submitted to the Faculty of Health Sciences, University of
the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for
the degree of Master of Medicine in the branch of Anaesthesia.

Johannesburg, 03 November 2014

DECLARATION

I, Magdalena Jaworska, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Anaesthesia at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

A handwritten signature in dark ink, appearing to read 'Magdalena Jaworska', with a large, stylized initial 'M'.

M. Jaworska

03 November 2014

To my family

PRESENTATIONS ARISING FROM THIS STUDY

1. Oral presentation at the South African Society of Anaesthesiologists (SASA) Congress, Port Elizabeth, March 2013.
2. Poster at the 5th All Africa Anaesthesia Congress (AAAC), Cairo, Egypt, April 2013.

ABSTRACT

Background: Post-operative pain is often undertreated, exposing patients to significant morbidity. The appropriate management of pain depends upon the accurate assessment thereof, however, this is difficult during general anaesthesia due to many confounders and thus intra-operative analgesia is administered according to multimodal “recipes” and changes in vital signs.

Aim: To determine whether intra-operative respiratory rate in a patient under general anaesthesia is a valid indicator of post-operative analgesic adequacy.

Method: The respiratory rates of 60 consenting adult female patients undergoing standardised general anaesthesia for elective breast surgery were measured. Post-operatively, each patient was assessed for the presence of pain using a Verbal Numeric Rating Scale (VNRS).

Results: Spearman correlation coefficient of 0.62 was calculated between the intra-operative respiratory rates and post-operative VNRS scores. A ROC curve (with AUC equals 0.77) was plotted to test the validity of respiratory rate as a predictor for post-operative pain, with a VNRS score greater than three indicating unacceptable pain. The suggested cut-off point for respiratory rate to predict unacceptable pain is greater than or equal to 17 breaths per minute.

Conclusion: The adequacy of post-operative analgesia may be predicted intra-operatively from the respiratory rate if patients are allowed to breathe spontaneously. This provides anaesthetists with a reliable, valid, affordable and easy method of titrating analgesia intra-operatively.

ACKNOWLEDGEMENTS

I am grateful to the following people:

Dr Des Lines for his expertise, encouragement and supervising of this project.

Professor Elena Libhaber and Dr Pieter le Roux for their assistance with the statistical analysis.

Mrs Juan Scribante and Mrs Helen Perrie for their advice and support during the planning of this study.

The staff of the General Surgery theatres and Post-operative recovery room, for their assistance with this project.

The Department of Anaesthesia, Chris Hani Baragwanath Academic Hospital, for their support and allowing me time out of theatre for this study.

TABLE OF CONTENTS

	Page
Title Page	i
Declaration	ii
Dedication	iii
Presentations arising from this study	iv
Abstract	v
Acknowledgements	vi
Table of Contents	vii
List of Figures	xii
List of Tables	xii
CHAPTER 1: OVERVIEW OF STUDY	1
1.1 Introduction	1
1.2 Problem statement	3
1.3 Aim	3
1.4 Objectives	3
1.4.1 Primary Objective	3
1.4.2 Secondary Objective	4
1.5 Definitions	4
1.6 Study design	6
1.7 Ethical considerations	6
1.7.1 Ethical clearance	6
1.7.2 Post-graduate approval	6

1.7.3	Change of title approval	6
1.7.4	Site approval	7
1.7.5	Patient consent	7
1.7.6	Declaration of Helsinki	7
1.7.7	Notification of Department of Anaesthesia	8
1.8	Summary of methodology	8
1.9	Significance of conducting this study	9
1.10	Research report outline	10
 CHAPTER 2: LITERATURE REVIEW		 11
2.1	Introduction	11
2.2	Incidence and complications of post-operative pain	11
2.3	Challenges of acute post-operative pain management	12
2.4	Pain assessment	14
2.4.1	Pain scales for acute and chronic pain	15
2.4.2	Acute pain assessment in awake adult patients	16
2.4.2.1	Numeric Rating Scale (NRS)	17
2.4.2.2	Visual Analogue Scale (VAS)	18
2.4.2.3	Verbal Rating Scale (VRS)	18
2.4.3	Comparison of the three pain assessment scales	19
2.4.4	Non-verbal patients: critically ill	20
2.4.5	Non-verbal patients: dementia and paediatrics	23
2.5	Assessment of pain under general anaesthesia	24
2.6	Current analgesic practice	27
2.7	New technologies	29

2.7.1	Skin conductance	31
2.7.2	Surgical Stress Index	33
2.7.3	Heart Rate Variability analysis and Analgesia/ Nociception Index	34
2.7.4	Pupillary Dilatation Reflex	36
2.7.5	The difference between Response Entropy and State Entropy	37
2.7.6	Near-Infrared Spectroscopy	38
2.7.7	Neuroimaging	39
2.7.8	Stress hormones	39
2.8	Pulmonary function under anaesthesia	40
2.9	Conclusion	45
 CHAPTER 3: METHODOLOGY		 47
3.1	Introduction	47
3.2	Study design	47
3.3	Study site	48
3.4	Study population	48
3.5	Study period	48
3.6	Ethical considerations	48
3.7	Notification of Department of Anaesthesia	49
3.8	Sample population and sampling method	49
3.9	Inclusion criteria	50
3.10	Exclusion criteria	50
3.11	Data collection	51

3.11.1 Patient information	52
3.11.2 Procedure in operating theatre	53
3.12 Validity and Reliability	55
3.13 Data analysis	56
3.14 Conclusion	57
 CHAPTER 4: RESULTS AND DISCUSSION	 58
4.1 Introduction	58
4.2 Sample size and patient refusal	58
4.3 Results relating to characteristics of study participants	59
4.3.1 Demographic characteristics	59
4.3.2 Clinical characteristics	60
4.3.3 Surgical characteristics	61
4.3.4 Chronic medication	62
4.3.5 Results of vital signs and VNRS	63
4.3.6 Results of analgesics administered intra-operatively	65
4.3.7 Results of rescue analgesics	66
4.3.8 Results of the presence & management of side-effects	66
4.4 Results related to the primary objective	67
4.5 Results related to the secondary objective	68
4.6 Summary of results	70
4.7 Discussion of results	70
4.7.1 Results relating to pain assessment scores	70
4.7.2 Results relating to the primary objective	71
4.7.3 Results relating to the secondary objective	72

4.8 Conclusion	73
CHAPTER 5: SUMMARY AND CONCLUSIONS	74
5.1 Introduction	74
5.2 Summary of study	74
5.3 Limitations of study	75
5.4 Recommendations for further research	76
5.5 Conclusions of study	77
APPENDICES	78
Appendix A: Ethics approval certificate	79
Appendix B: Post-Graduate Committee approval certificate	80
Appendix C: Post-Graduate Committee approval of change of title	81
Appendix D: Permission from Medical Advisory Committee	82
Appendix E: Patient information sheet	83
Appendix F: Informed consent form	84
Appendix G: Data collection sheet	85
LIST OF REFERENCES	86

LIST OF FIGURES

Figure 2	Commonly used uni-dimensional pain intensity scales: Visual Analogue Scale (VAS), Numeric Rating Scale (NRS) and Verbal Rating Scale (VRS)	17
Figure 3	Behavioural Pain Scale	21
Figure 4.1	Correlation of respiratory rate and pain score (VNRS assessment)	68
Figure 4.2	Receiver-operating characteristic (ROC) curve showing the relationship between sensitivity and 100-specificity in determining the value of the respiratory rate that predicts a VNRS >3	69

LIST OF TABLES

Table 1.1	Pre-operative physical status classification of patients according to the American Society of Anaesthesiologists	5
Table 4.1	Demographic characteristics of sample population	59
Table 4.2	Clinical characteristics of sample population	60
Table 4.3	Surgical characteristics of sample population	61
Table 4.4	Chronic medication taken by sample population	62
Table 4.5	Values of vital signs and post-operative VNRS	63
Table 4.6	The distribution of intra-operative vital signs versus VNRS <3 and VNRS >3	64
Table 4.7	Analgesic drugs administered intra-operatively	65
Table 4.8	Drugs administered as rescue analgesia	66

CHAPTER 1: OVERVIEW OF STUDY

1.1 Introduction

Post-operative pain is often undertreated, exposing patients to numerous adverse physiological and psychological consequences, such as suffering and prolonged recovery, medical and surgical morbidity, in addition to financial drawbacks for caregivers (1-5).

The appropriate management of pain in an individual patient depends in part upon the accurate assessment thereof (5). Numerous pain assessment tools, which have been validated in the literature, are available for use in awake patients and regard the patient's self-report as the most reliable indicator of pain (1).

Techniques for use in patients who are unable to self-report, for example critically ill patients, those with advanced dementia, and preverbal paediatric patients, have also been developed (5-7). These tools regard the use of behavioral parameters, such as facial grimaces, restlessness and vocalisation, as indicators of pain (5,6). These pain assessment tools do not utilise vital signs (heart rate, mean arterial pressure, respiratory rate) in the assessment of pain status, as these are considered to be non-specific and lacking in sensitivity (5,6,8). However, it is recommended that vital signs be used to complement behavioral indicators (5,8,9).

General anaesthesia precludes the use of behavioral parameters as indicators of pain, and thus the assessment of pain in patients under general anaesthesia is difficult.

Current experimental techniques for the assessment of intra-operative nociception exist. These monitors allow for the real-time measurement of certain aspects of sympathetic activation in response to surgical stimulation, however, trial results have been inconsistent and they do not predict the adequacy of post-operative pain relief. Also, it is unlikely that these methods will become readily available in resource-constrained facilities.

In studies of human physiology on awake healthy adults, respiratory rate, blood pressure and heart rate have been shown to increase in response to a noxious stimulus due to activation of the autonomic nervous system (6,9). Current clinical practice advocates the use of multimodal analgesic “recipes” which are modified according to a patient’s vital signs (1). However, disease, medications and changes in physiologic status as well as individual variation in nociception and response to analgesics, obtunded autonomic responses under general anesthesia and variable nociception among surgical procedures confound estimates (1,6,9).

1.2 Problem statement

Owing to the lack of methods of assessing the adequacy of intra-operative analgesia, there is a need for the development of a technique that is simple to use, affordable, reliable and valid for the assessment of pain in patients under general anaesthesia, without the need for sophisticated equipment. Therefore, the correlation between intra-operative respiratory rate in a spontaneously breathing patient under general anaesthesia and post-operative analgesia warrants investigation to determine whether this parameter may be used as a single reliable and valid indicator of pain.

1.3 Aim

The aim of this investigation is to determine whether intra-operative respiratory rate in a female patient under general anaesthesia for elective breast surgery at Chris Hani Baragwanath Academic Hospital is a valid indicator of the adequacy of post-operative analgesia.

1.4 Objectives

1.4.1 Primary objective

To determine the correlation between intra-operative respiratory rate in a spontaneously breathing patient under general anaesthesia at the end of a surgical procedure, and post-operative Verbal Numeric Rating Scale (VNRS) score after emergence from general anaesthesia.

1.4.2 Secondary objective

To determine the threshold intra-operative respiratory rate in spontaneously breathing patients under general anaesthesia, which best predicts adequate post-operative analgesia, as determined by data analysis.

1.5 Definitions

The following terms are used in the study:

1.5.1 ASA classification:

A classification system of physical status developed by the American Society of Anaesthesiologists (ASA) for use in assessing a patient pre-operatively, to predict operative risk (see **Table 1.1**) (10).

Table 1.1: Pre-operative physical status classification of patients according to the American Society of Anaesthesiologists (10).

ASA Class	Definition
1	A normal healthy patient.
2	A patient with mild systemic disease (no functional limitations).
3	A patient with severe systemic disease (some functional limitations).
4	A patient with severe systemic disease that is a constant threat to life (functionality incapacitated).
5	A moribund patient who is not expected to survive without the operation.
6	A brain-dead patient whose organs are being removed for donor purposes.
E	If the procedure is an emergency, the physical status is followed by “E”.

1.5.2 Verbal Numeric Rating Scale (VNRS):

This scale is a pain assessment tool that allows for objective measurement of pain intensity. It consists of a zero to 10 verbal scale. The patient is requested to rate the severity of his or her pain verbally, with zero representing no pain and 10 representing the worst possible pain (1).

The advantages of this scale are that it requires only a brief explanation to patients and is easily understood. It is also useful for research as it allows for simple documentation, reporting and comparison (1).

1.6 Study design

This investigation is a prospective observational pilot study.

1.7 Ethical considerations

1.7.1 Ethical clearance

This study has been approved by the University of the Witwatersrand, Human Research Ethics Committee (**Appendix A**).

1.7.2 Post-graduate approval

The study has been approved by the Post-Graduate Committee of the University of the Witwatersrand, Faculty of Health Sciences (**Appendix B**).

1.7.3 Change of title approval

The change of title of this study has been approved by the Post-Graduate Committee of the University of the Witwatersrand (**Appendix C**).

1.7.4 Site approval

Permission to conduct this study has been granted by the Medical Advisory Committee at Chris Hani Baragwanath Academic Hospital (**Appendix D**).

1.7.5 Patient consent

Patients suitable for inclusion in the study were invited to participate. The study aim and protocol were explained to them with the assistance of a translator where required. Patients received a printed document in English (**Appendix E**) detailing the purpose of the study, the nature of their involvement, the right to refuse to participate without repercussions to their care, as well as the right to withdraw from the study at any time. A 24-hour contact number was supplied should they require further information.

The researcher, together with a translator, provided verbal information in a language that the patient could understand if they were not fluent in English, or were unable to read the document. Patients were requested to sign a consent document if they agreed to participate in the study (**Appendix F**). The study participants were then interviewed and educated about the Verbal Numeric Rating Scale (VNRS). Patient anonymity was ensured by a coding system known only to the investigator.

1.7.6 Declaration of Helsinki

This study has been structured in accordance with the principles outlined in the Declaration of Helsinki (11).

1.7.7 Notification of Department of Anaesthesia

Members of the Department of Anaesthesia at CHBAH were notified about the study prior to its commencement. Anaesthetists allocated to the elective breast surgery lists were made aware of which patients were study participants, and were requested to deliver a specific general anaesthetic technique, which is in accordance with routine practice but which would allow for standardization. Anaesthetists not willing to be involved with the study were requested to contact the consultant responsible for list allocation.

1.8 Summary of methodology

In this prospective observational study 60 consenting female patients, aged 18 to 60 years, ASA 1 to 2, scheduled for elective breast surgery lasting more than one hour were enrolled using consecutive convenience sampling. Patient demographics, medical history, baseline vital signs and baseline VNRS score were recorded.

The attending anaesthetist proceeded with the delivery of a standardised general anaesthesia protocol in every study participant. Intravenous access was obtained and routine intra-operative monitors were applied. Anaesthesia was induced with propofol and fentanyl, and maintained with sevoflurane or isoflurane through a circle system. Patients were allowed to breathe spontaneously via a laryngeal mask airway, but received assisted ventilation if required to maintain $E_t\text{CO}_2$ within 30 to 55 mmHg. The analgesic strategy was left to the discretion of the attending anaesthetist. Following emergence,

patients were taken to the post-operative recovery room where they received routine post-operative care.

Intra-operatively, the dosages of analgesic drugs administered were recorded. During wound closure respiratory rate, $E_t\text{CO}_2$, heart rate and non-invasive mean blood pressure were recorded. Post-operatively, each patient was assessed for the presence of pain using the same VNRS, as soon as able to verbalise and again before discharge from the post-operative recovery room. Additional rescue analgesia was administered if required as indicated by a VNRS greater than three. Side effects were managed and recorded.

1.9 Significance of study

The significance of this study is that intra-operative respiratory rate is a reliable and valid method, which is affordable and easy to implement, of predicting the adequacy of post-operative analgesia.

Despite the difficulty inherent to measuring pain, the use of intra-operative respiratory rate to guide the administration of analgesics, may allow for the provision of efficient pain relief, with dosages titrated to individual cases, thereby minimizing the incidence of adverse events related to over- and undertreatment. This technique may improve the quality of pain relief in the immediate post-operative period before the patient returns to the ward and receives subsequent doses of analgesics.

1.10 Research report outline

This research report will comprise of the following chapters:

- Chapter One:** an introduction to the study, including the aim and objectives of the study, and a brief summary of the methodology used.
- Chapter Two:** a review of the literature pertinent to topics raised by the study.
- Chapter Three:** a detailed description of the methodology used for the study.
- Chapter Four:** the results of the study and their interpretation.
- Chapter Five:** summary and conclusions of the study.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

Relief of pain is not only the duty of the compassionate health care worker, but is also a patient's right (1,12). Despite advances in the understanding of the physiology of acute pain, the availability of clinical practice guidelines for pain management, the abundant analgesic armamentarium and novel methods of drug administration, the management and alleviation of post-operative pain continues to be unsatisfactory (2-4).

2.2 Incidence and complications of post-operative pain

The presence of moderate to severe pain upon awakening from anaesthesia has been demonstrated in multiple studies (13-16). Although the quoted incidence varies considerably (two to 70%) and is dependent on several patient and procedural factors, there is no doubt that unrelieved acute post-operative pain contributes to numerous adverse psychological and physiological consequences for patients, in addition to financial drawbacks for caregivers (2-4).

Appropriate pain management is essential for patient convalescence and comfort in the post-operative period (4,16). Inadequate pain relief increases complication rates and delays hospital discharge (14,17,18). Acute pain evokes a stress response, characterized by catabolism, sympathetic stimulation and immunosuppression, which activates a neuro-humoral cascade with multisystemic effects (1). Poorly managed pain increases

myocardial demand and predisposes to ischaemia. Pain limits coughing and ambulation, increasing the risks for respiratory and thromboembolic complications. Depression of the immune response interferes with wound healing and has been associated with an increased risk of metastases (3,18,19). Acute pain has detrimental effects on patients' sleep and mood, leading to fatigue, impaired function and depression (13,18,20). In addition, there is ample evidence incriminating severe acute post-operative pain with the development of chronic post-surgical pain (1,14,21,22).

Clinical guidelines emphasize the need for improved analgesia to enhance patient recovery and quality of life, as well as reduce medical and surgical morbidity, and healthcare costs (1,2,16).

2.3 Challenges of acute post-operative pain management

The International Association for the Study of Pain defines pain as an “unpleasant sensory and emotional experience, associated with actual or potential tissue damage or described in terms of such damage” (1). Hence pain is a subjective sensation, and therefore encompasses a variety of biopsychosocial aspects. Gender, age, cultural background and the environment impact on the response to pain (1,23). Pain is associated with psychological and emotional effects such as fear, helplessness and anxiety (3,4,22-24). The perception of pain is modified by prior pain experiences and expectations (1,18). Anaesthetic technique, type of surgical procedure and the occurrence of side-effects also influence the experience of pain (14).

Patients do expect pain after surgery, but the actual pain experienced is often of significantly greater intensity than anticipated (4,17). Also, there may be a reluctance of patients to inform staff of their pain (17). Studies have shown that health care workers frequently underestimate patients' pain levels and the impact of this suffering (4,18,20,21). Discrepancies between patients' reports and caregivers' perception of pain, leads to inadequate administration of analgesics as well as uncertainty regarding analgesic efficacy (3,24,25).

Anaesthetists are responsible for the administration of analgesia intra-operatively to reduce pain associated with surgical procedures. However, many pain management regimens are not appropriately individualised according to patient factors and type of surgery, predisposing patients to the complications of over- and under-dosing (2,4).

Investigations into the barriers of effective treatment of acute pain suggest an array of potential factors, with inadequate assessment of pain cited most frequently (2-4,24). Improving the quality of post-operative pain is a multifactorial task (26). The ability to evaluate pain accurately may lead to an improved approach to acute pain management, which meets the needs of individual patients and enhances both the efficacy and safety of analgesic therapies (2).

2.4 Pain assessment

The American Pain Society has designated pain as the fifth vital sign and recommends the incorporation of pain assessment into routine vital sign monitoring (1,8,25). Furthermore, current guidelines for good pain management practice state that pain must be assessed and documented on a regular basis (1,3).

Assessment of pain confers heightened awareness of patients' pain status and is crucial for obtaining efficient analgesia as patients have an improved means by which to express their pain and need for pain relief (3,25). Moreover, documentation of pain assessment scores has been shown to lead to better communication between various health care professionals about pain management (3).

Pain measurement is difficult due to the multifaceted and complex nature of pain, and is vulnerable to bias by both the patient and the health care worker (25,27). Various validated pain assessment tools have been developed which attempt to quantify and convert the personal experience of pain into an impartial result (1,17,23,25,28).

Objectively dissecting the subjective affliction of pain is a formidable task, consequently the pain evaluation techniques pose a number of measurement challenges. Developmental age, cognitive function and emotional status of the patient, in addition to type of pain, must be taken into account in the

evaluation of pain, and thus determine the type of pain assessment tool selected (1,29).

In the current culture of evidence-based medicine, it is important for clinicians and researchers to utilise sensitive and accurate pain outcome measures to determine whether meaningful changes have occurred (27). A plethora of trials have been conducted comparing and contrasting diverse pain scoring systems, with disparate sample sizes, methodologies and outcome measures, yielding discrepancies in statistically and clinically significant effects (17,23,25,27,28). The use of complex measurement tools that preserve scientific validity at the expense of compliance do not serve patients' needs. Effective implementation of pain measurement initiatives requires simple user-friendly tools (25,28).

2.4.1 Pain scales for acute and chronic pain

Acute and chronic pain differ in their aetiology, pathophysiology and management and likewise, require separate pain assessment techniques (27,29). For acute pain, determining location, temporal aspects, pain intensity and pain-related interference in activities, allows to characterise the pain and evaluate the effects of treatment (29). Acute pain intensity can be reliably assessed, at rest and on movement, by uni-dimensional scales (27,29). These scales provide fast measures of pain that can be conducted multiple times with minimal administrative effort, and are easily understood by the patient.

The complex nature of chronic pain requires the use of multi-dimensional pain scales, which measure distinct qualitative elements of pain and the impact on physical, emotional and social functions (1,27,29). Chronic pain therapy aims to improve health-related quality of life, thus the reduction of chronic pain intensity is not the only objective. In contrast, acute post-operative pain therapy primarily focuses on pain intensity reduction, which allows for improved physical and mental functioning (20).

2.4.2 Acute pain assessment in awake adult patients

Numerous pain assessment tools are available for use in awake adult patients and regard the patient's self-report as the most reliable indicator of pain (1).

The three most studied and most commonly used uni-dimensional scales to assess acute post-operative pain include the Visual Analogue Scale (VAS), Numeric Rating Scale (NRS) and Verbal Rating Scale (VRS) (See **Figure 2**) (17,23,25,27-29). These function best for the patient's subjective sensation of pain intensity, however, each has its own strengths and weaknesses. They may be used for worst or least pain at rest and on movement at the time of assessment, or average pain determined retrospectively over several hours or days (29,30).

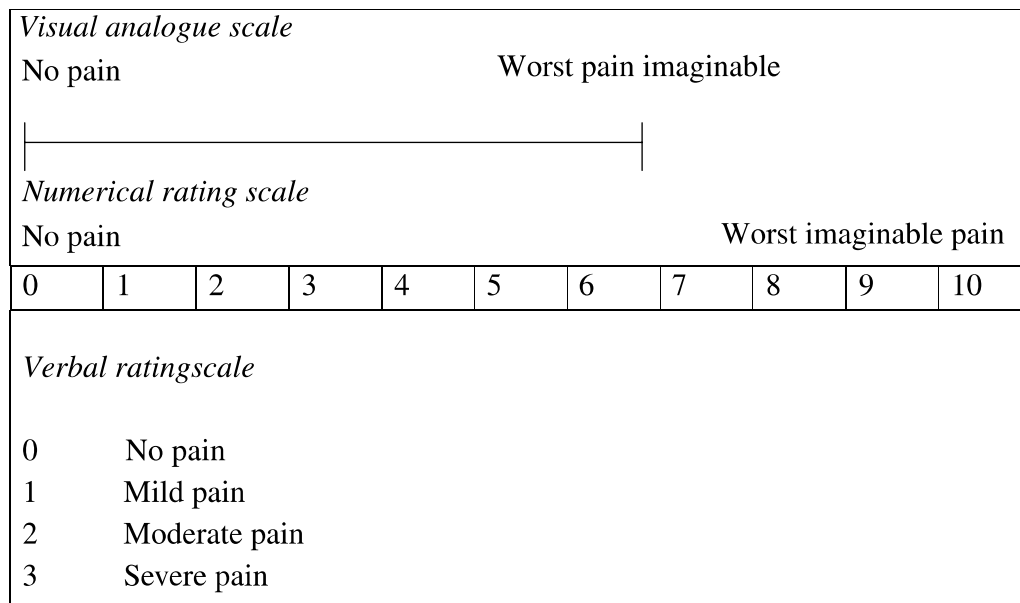


Figure 2: Commonly used uni-dimensional pain intensity scales: Visual Analogue Scale (VAS), Numeric Rating Scale (NRS) and Verbal Rating Scale (VRS) (23).

2.4.2.1 Numeric Rating Scale (NRS)

This pain assessment scale consists of a zero to 10 score, with zero being described as “no pain” and 10 described as “worst pain imaginable”. The patient is requested to rate the severity of his or her pain, using whole numbers (11 integers including zero) (25). (See **Figure 2**).

The NRS is a tool that enjoys widespread clinical use due to its simplicity of application (25). The advantages of this scale are that it requires only a brief explanation to patients and is easily understood. It may be administered graphically or verbally, thus not requiring patient mobility nor carrying of specific tools (1,23,27). It is also useful for research as it allows for simple documentation, reporting and comparison.

2.4.2.2 Visual Analogue Scale (VAS)

The patient is asked to mark anywhere along a 100 mm straight line to indicate their current pain intensity, where the end points are the extremes of no pain and worst possible pain. The result is presented as a ratio (1,25). (See **Figure 2**).

To assist in the scoring process, slide ruler-like devices have been developed. VAS measurement is accurate but it requires the assessing health care worker to carry the instrument, and some patients do not understand the tool (1,27).

2.4.2.3 Verbal Rating Scale (VRS)

Individuals who have trouble translating their pain experience into a numerical value can use the VRS. The anchors are replaced by descriptors, which categorise pain into none, mild, moderate or severe (1). For ease of recording, these adjectives are assigned numbers. These rank numbers can lead to the misapprehension that intervals between each descriptor are equal, but this is not the case and could be a source of error (23). (See **Figure 2**).

This type of measure has several statistical drawbacks and is usually used only when patient characteristics require it. This tool's effectiveness is limited in a multilingual society (1,27).

2.4.3 Comparison of the three pain assessment scales

All three pain rating scales are valid, reliable and appropriate for use in the post-operative setting, the choice dependent on subjective preferences (17,23). The evidence suggests that patients are able to use them to communicate their pain experience and their response to treatment.

NRS and VAS have been utilised widely by clinical investigators to quantify acute pain in the post-operative period, and their reliability and reproducibility have been studied extensively (23,25,28,30). NRS and VAS agree well and are equally sensitive in assessing acute pain intensity. Both the NRS and VAS have been shown to be superior in detecting changes in pain intensity than VRS (25,28,29).

NRS is more practical than VAS, easier to understand for most patients, and does not need clear vision, dexterity, additional devices or writing materials (23,25,28,29). It has been demonstrated that both patients and clinicians prefer the NRS to the VAS or VRS, and it is also the most robust tool for research (23,28).

Several studies have used the threshold value of NRS score of less than three or VAS score of less than 30 mm as the optimal cut-off point between mild and moderate pain, representing the upper limit of tolerable post-operative pain or analgesic success (15,16). This division allows separation of patients into groups who are in need of further analgesic intervention (moderate and severe pain) and those who are not (mild pain). Similarly, “no

worse than mild pain” on VRS confirms clinical judgment as to the need for further intervention or documentation that the patients’ goals for analgesia have been achieved (13,20,25). These cut-off points serve only as a guideline and pain treatment should be tailored to individual needs. However, an inappropriate cut-off point on a pain treatment protocol may carry a risk of over- or undertreatment (20).

2.4.4 Non-verbal patients: critically ill

The management of pain is an important and complex aspect of patient care in the Intensive Care Unit (ICU). Pain is difficult to measure in ICU patients where many factors compromise the patient’s ability to verbalise or point at visual pain scales (5,7,8). Individuals who are unable to communicate their discomfort are at greater risk for inadequate analgesia and current evidence supports claims that pain in sedated, unconscious ICU patients is underrated and undertreated when pain assessments are not routinely performed (7,12).

Research suggests that pain should be measured systematically using a validated tool which matches the communication capabilities of the patient (5,8). Pain assessment tools for use in ICU on sedated critically ill patients who are unable to self-report have been developed (5-7). Evaluation of the impact of pain assessment in ICU patients has been found to be associated with reduced pain and agitation, and reduced duration of mechanical ventilation and nosocomial infections (5).

Since the autonomic nervous system is activated during an acute painful event, the ensuing observable behavioral and physiological indicators are considered suggestive of the presence of discomfort or pain and become important indices for pain assessment in non-verbal patients, however, physiological parameters have received criticism (5,6,8,9).

Some examples of pain assessment tools for use in critically ill patients include the Behavioral Pain Scale (5,6,7,12) (see **Figure 3**), Critical Care Pain Observation Tool (5,8,12) and Pain Assessment and Intervention Notation Algorithm (6).

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g. brow lowering)	2
	Fully tightened (e.g. eyelid closing)	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing with movement	2
	Fighting ventilator	3
	Unable to control ventilation	4

Figure 3: Behavioral Pain Scale (7).

These tools regard the use of behavioral parameters, such as facial expression, body movements and ventilator compliance, as valid and reliable indicators of pain levels (5,6,8). The pain assessment instruments do not utilise physiological indicators in the assessment of pain status, as these are

considered to be non-specific and lacking in sensitivity to pain (5,6,8). However, it is recommended that vital signs be used to complement behavioral indicators (5,8,9).

Findings regarding the use of vital signs for pain assessment are limited, however, increases in arterial blood pressure, heart rate and respiratory rate are considered the most relevant physiological cues associated with pain (8). Transcutaneous oxygen saturation (SpO₂), end-tidal CO₂, perspiration, pallor and tearing have also been anecdotally associated with acute pain, but are not supported by any empirical data in the literature (6,8,9,12).

Indeed, haemodynamic changes can occur for reasons other than pain, especially in the critically ill patient (5). Cardiorespiratory fluctuations may be attributed to underlying pathological conditions, homeostatic alterations as well as the administration of medications and performance of routine nursing procedures (7,9). Vital signs in ICU patients are inconsistent as changes may occur in response to noxious as well as non-noxious stimuli, with respiratory rate demonstrating the least variability to non-painful stimuli (9). In addition, normal vital signs may not be indicative of the absence of pain. However, it has been recommended that a change in vital signs should prompt a further probe into the cause for this change, with an assessment of pain being cited as part of the search (5,8,9).

Problems with the behavioral aspects of ICU pain assessment tools have been identified. Unconscious, delirious and heavily sedated patients are less

able to exhibit the behaviors on the tool (5,9). Likewise, none of these tools can be recommended to assess pain in patients with spinal injuries and those receiving neuromuscular blocking agents due to depressed motor activity (5,8). In these instances, changes in physiological parameters should be used as a cue to begin further assessment of pain or other stressors in critically ill nonverbal adults when behavioral indicators are no longer available (9,12).

2.4.5 Non-verbal patients: dementia and paediatrics

The inability of patients with advanced dementia and preverbal paediatric patients to communicate their pain and discomfort because of cognitive, developmental or physiologic factors constitutes a major barrier for them being adequately assessed for pain and achieving appropriate pain management interventions (12,18,27,29). Validated pain assessment techniques for use in these challenging populations have also been developed (1,5,6).

Behavioral parameters, such as facial or bodily movement, and vocalisation are used as proxy measurements of pain (12,27). Credible information can also be obtained from a caregiver or parent, where familiarity with the patient's behaviour can assist in identifying changes that may be indicators of pain presence. A regular search for potential causes of pain and discomfort is advised. Alternatively, an empiric analgesic trial is recommended if there are pathologic conditions present, as this may be diagnostic as well as therapeutic (12).

Physiologic variables such as heart rate, respiratory rate and SpO₂, although used often, are not sensitive for discriminating pain from other sources of distress in these populations and may also be affected by disease, medications and changes in physiologic status (12).

2.5 Assessment of pain under general anaesthesia

General anaesthesia for surgical procedures aims to provide suppression of consciousness (hypnosis), analgesia and in certain cases, muscle relaxation (14). Insufficient hypnosis (depth of anaesthesia) as well as acute pain will evoke sympathetic adrenergic activity. Techniques for the assessment of depth of hypnosis have been developed, but these are lacking for the determination of analgesic adequacy. At the termination of surgery, hypnosis is no longer required, whereas pain persists into the post-operative period, the perception of which is heightened by the return of the patient's consciousness (16).

In the daily practice of anaesthesia, the differentiation between pain-evoked reactions and insufficient depth of anaesthesia causes considerable difficulties. Patient safety and comfort are strongly dependent on reliable technical monitoring as well as on interpretation of indirect clinical signs (14,31).

The monitoring of evoked neurophysiological responses may elucidate the adequacy of the hypnotic state, and consequently the Bispectral Index,

Entropy and auditory evoked potentials have been developed in pursuit of assessing the anaesthetic effects on brain activity (14,32-34). Gas analysis of expired concentrations of inhalational anaesthetics also provides information regarding anaesthetic depth (32).

Both insufficient and excessive depth of hypnosis due to inappropriate anaesthetic drug delivery may compromise patients' outcome. Studies highlight that titrating hypnotics to values derived from depth of anaesthesia monitoring may help to decrease the occurrence of awareness, reduce drug consumption and shorten recovery times when compared with standard practice protocol (31,35). Hence, individualising anaesthesia to minimise both over- and underdosage of anaesthetic drugs during general anaesthesia is the goal of modern anaesthesiologists (35).

In contrast, no equipment is currently available for monitoring pain intensity to assist in titrating analgesics during general anaesthesia (35). In the hierarchy of indicators of pain, both the patients' self-report and behavioural indicators are unavailable under general anaesthesia, thus the assessment of analgesic adequacy is problematic (8,12). The anaesthetist is consequently left to gauge the occurrence of pain-induced responses from routinely monitored physiological variables and indirect clinical signs (14). However, the lack of a systematic and standardised method for evaluating pain levels intra-operatively prevents the accurate identification of escalating pain and therefore guiding of analgesia to avoid exposing patients to the detrimental consequences of pain (5).

Patients under general anaesthesia require continuous monitoring, hence vital signs are readily available (14). Physiological responses to intra-operative stimuli as a result of sympathetic stimulation do not provide a clear distinction between reactions induced by pain or insufficient depth of anaesthesia (14,31). Notable signs of sympathetic over-activity include lacrimation, sweating, increase in pupil size, reflex movements, and increased heart rate, arterial blood pressure and respiratory rate. The sympathetic response is usually proportional to the intensity of the noxious stimulus but there is great individual variability, due to differences in physiological factors, disease and medications (6,9,14).

Attempts at identifying and separating indicators of pain from indicators of insufficient depth of anaesthesia have been made with varying results (14,35). No variable is considered entirely specific for either intra-operative pain or depth of anaesthesia. Changes in respiratory pattern, central haemodynamics, lacrimation and skin-associated responses (temperature, colour and moisture) are considered more suggestive of pain than depth of anaesthesia. While the occurrence of grimaces, attempted movements and eye reactions is considered more indicative of insufficient depth of anaesthesia (14,31).

Historically, non-specific haemodynamic, respiratory, muscular as well as autonomic responses to intra-operative stimuli were originally suggested by Guedel (1920) as relevant indicators of depth of anaesthesia (14). However, many modern anaesthetic agents have overlapping analgesic and sedative

properties and may therefore mask autonomic vegetative physiological responses, thereby diminishing the clinical reliability of differentiating monitored variables. In addition, different anaesthetic agents are commonly combined so that the undesirable, dose-dependent side-effects of each single drug can be minimised. Such polypharmacy may further complicate the monitoring of hypnotic state based on autonomic clinical signs because pain-evoked responses may be concealed (14).

2.6 Current analgesic practice

Current clinical practice advocates the implementation of procedure-specific, evidence-based multimodal pain management protocols in the peri-operative period, in combination with fast-track recovery strategies to obtain the desired improvements in patient outcomes (1,2).

Different types of surgical procedures have their own unique post-operative pain characteristics and clinical consequences (2). In addition, analgesic drugs or techniques may have different side-effect profiles depending on the type of surgical procedure. The synergism achieved by combining analgesics from different pharmacologic classes aims to provide improved analgesia due to interruption of pain transmission at various points in the nociceptive pathways (2,4). Multimodal analgesic techniques are highly recommended to reduce the risk of chronic post-surgical pain (22).

Considerable differences in pain perception and response to anaesthetic and analgesic drugs exist. Pharmacodynamic and pharmacokinetic mechanisms related to age, gender, body compartment sizes, and genotype may all influence the response of the individual patient and explain major differences in dose requirements (4,22). Furthermore, combination therapies have their own unique side-effect profiles, which may be exacerbated when they are administered as a part of a multimodal regimen after surgery (2). Thus, injudicious use of all analgesic modalities is not justified as the patient is subjected to the potential adverse effects resulting from drug interactions in addition to a greater spectrum of side effects (2).

Analgesic titration in the post-operative period is also problematic. Overly aggressive use of opioid analgesics in low pain responders has contributed to significant morbidity and even mortalities after surgery (2). Studies have revealed that patients with high initial pain scores in the immediate post-operative period required greater doses of morphine to achieve pain relief and necessitated rescue morphine more frequently than those with lower pain scores (36,37). In addition, such patients reported moderate to severe pain more frequently in their post-operative course, poorer quality of sleep, and higher pain scores at 24 hours (38). Effective analgesia in the early post-operative period is of major importance because it determines the quality of the subsequent analgesia and affects the patient's overall satisfaction about pain management (16,38).

Accomplishing effective analgesic titration in the immediate post-operative period is further hindered by reliably evaluating post-operative analgesia using patients' self-reporting pain scales (16). Initial evaluation is complicated by the residual perceptual cognitive impairment associated with general anaesthesia. Many patients are unable to clearly express their pain level in the immediate post-operative period, and to discriminate between objective pain and discomfort feelings owing to opioid-induced sedation, blurred vision, post-operative nausea and vomiting or anxiety, making it difficult to use these scales and reducing their clinical relevance (16).

In conclusion, the deficiency of reliable assessment of intra-operative pain intensity has been highlighted. Rapid control of acute pain at the time a patient recovers consciousness is a critical step in achieving effective analgesia in the early post-operative period and is dependent on the accuracy of pain level evaluation (2,16).

2.7 New technologies

The field of acute pain management would benefit from objective cooperation-independent monitors of pain, and new technological approaches assessing diverse parameters of sympathetic tone, are being studied for this purpose (27,39). The balance of intra-operative pain or nociceptive stimulation versus analgesic dose effect is a major focus of ongoing research (19).

Current experimental techniques for the assessment of nociception include the use of:

- Skin conductance
- Surgical Stress Index
- Heart Rate Variability analysis and Analgesia/Nociception Index
- Pupillary Dilatation Reflex
- The difference between Response Entropy and State Entropy
- Near-Infrared Spectroscopy
- Neuroimaging
- Stress hormones

These monitors allow for the real-time measurement of certain aspects of sympathetic activation in response to surgical stimulation, however, these parameters indicate general autonomic activity, which can be influenced by many factors other than pain, such as other forms of arousal, and treatments may directly impact those physiologic variables, reducing their reliability as surrogate measures of pain (27).

Furthermore, trial results have been inconsistent and these techniques do not predict the adequacy of post-operative pain relief. More trials would have to be performed before these modalities become validated for the use of pain assessment in patients under general anaesthesia (9,19,35,43). Also, it is unlikely that these methods will become readily available in resource-constrained facilities.

These techniques may become important future tools for tailoring the use of analgesic administration in order to reduce pain as well as its complications, while keeping side effects to a minimum (19). Although these different monitors are based on the assessment of autonomic responses to nociception, they are not simply exchangeable. Hence, research may need to be directed to identify the ideal monitor or combination thereof for specific clinical settings (41).

2.7.1 Skin conductance

Pain and emotion may stimulate the sympathetic nervous system to cause sweating that is independent of environmental temperatures within the normal range. Skin sympathetic nerves release acetylcholine, which in turn activates sweat glands to release sweat. When this sweat reaches the skin surface, skin resistance is reduced and skin conductance increases. Once the sweat is reabsorbed, skin conductance decreases again. This creates a series of conductance peaks, the sizes of which are proportional to the magnitude of skin sympathetic nerve activity (19,33,34,39,40).

A skin conductance algesimeter (SCA) has been developed (Med-Storm[®], Norway) to analyse fluctuations in skin conductance per second as a surrogate for changes in pain intensity (19,39). The measurement is performed using electrodes attached to palmar or plantar skin, which transmit signals to the measurement unit, where they are processed and then displayed.

Testing in patients under general anaesthesia revealed good correlation of skin conductance peaks with tetanic stimulation without analgesia. Subsequent peaks decreased progressively with increasing doses of analgesia and continued stimulation (19). In addition, skin conductance fluctuations correlated, albeit with variable accuracy, with post-operative pain scores of patients in the recovery room as well as in patients in ICU as assessed by numerical rating scales, and equated to episodes of noxious stimulation in mechanically ventilated patients (19,39,40). In both groups of patients, skin conductance fluctuations were attenuated with the administration of analgesics (19,39).

The advantages of the SCA include fast response time, continuous and objective measurement, and the device compares favourably with other currently available methods for assessing pain (19). There are no significant differences in the inter-individual and intra-individual variability in the skin conductance responses in patients of all ages. Also, the device is not influenced by neuromuscular blockade, adrenergic receptor agonists nor circulatory changes (19).

However, the SCA is susceptible to electromagnetic interference and movement artifact. Also, measurements are unreliable when drugs, such as anti-cholinergics or α_2 -agonists, which have effects on the autonomic nervous system, have been used (19,39). Other types of sympathetic nervous activation, namely nausea and vomiting, as well as suppression, such as excessive depth of anaesthesia, will also influence the SCA index (19,39).

Use of the device is contraindicated in patients with pacemakers, as well as placement of electrodes over inflamed or injured skin (19,39). Results may be unreliable at extreme ranges of patient temperatures, in patients with autonomic neuropathy, and with the use of regional anaesthesia.

In conscious subjects, sympathetic tone is highly volatile and influenced not only by pain, but a diversity of factors, such as anxiety, confusion, noise level and drugs. Hence measured fluctuations may not always reflect pain, but other confounders (39,41).

2.7.2 Surgical Stress Index

Surgical Stress Index (SSI) is a multivariate index utilising a combined assessment of cardiac and peripheral sympathetic tone (35,40). The sum of the normalised pulse beat interval (similar to Heart Rate Variability) and peripheral plethysmographic pulse wave analysis, both obtained from a pulse oximeter, are computed to give a score from zero to 100. A value of zero represents a low stress level and a value of 100 represents a high stress level. A target span of SSI between 20 to 50 during general anaesthesia has been suggested, however, an optimal range of SSI has not been recommended yet (35).

It has been shown that SSI correlates positively to surgical nociceptive stimuli and negatively to analgesic drug concentration during general anaesthesia (35). Also, SSI has been used to guide intra-operative analgesic

administration, which resulted in a significant reduction of analgesic consumption (thus preventing overdosing), more stable haemodynamics and shorter recovery times when compared to standard clinical practice (35).

In haemodynamically unstable patients, as well as with the use of cardio- and vasoactive drugs and regional anaesthesia, the rationale for using these haemodynamic measures to monitor noxious stimuli is questionable (19).

Both skin conductance and SSI have shown promising results in the assessment of nociception in unconscious or sedated patients, but when tested in awake subjects, low sensitivity and specificity was demonstrated (40). Thus, failure to reflect acute post-operative pain with reasonable accuracy, may suggest that these techniques are not suitable for conscious patients.

2.7.3 Heart Rate Variability analysis and Analgesia/

Nociception Index

Several studies have demonstrated the use of Heart Rate Variability (HRV) as an indicator of cardiac sympathetic activity (43). Sinus arrhythmia is a normal phenomenon whereby the duration between successive R waves (R-R interval) on the electrocardiogram (ECG) varies in relation to respiration. This method samples a series of R-R intervals from the ECG at regular time periods and utilises an algorithm to analyse the variation in sinus arrhythmia. This variation has been shown to follow a constant pattern in patients under

general anaesthesia without any surgical stimuli. However, this pattern becomes erratic when painful surgical stimuli are applied, irrespective of the depth of anaesthesia (43).

Analgesia/Nociception Index (ANI) is a non-invasive index calculated from Heart Rate Variability, which reflects the analgesia/nociception balance during general anaesthesia (15,41). It is based on ECG data derived from two single-use ANI electrodes applied in V1 and V5 positions to the chest. The ANI is computed from an ECG analogue output from the patient monitor and also incorporates the patient's respiratory rate as a potential confounder. It is displayed as a score from zero to 100, with low values reflecting low and high values reflecting high parasympathetic predominance in autonomic cardiac control (15,41).

Advantages of this technique consist of continuous real-time and non-invasive analysis. Potential limitations include erroneous results due to electromagnetic interference, movement artifact and electrode or lead detachment (43). Furthermore, arrhythmias, autonomic nervous system disorders and vasoactive drugs may impact upon the results. HRV is influenced by multiple other factors including age, different effects of hypnotics and analgesics, changing autonomic or haemodynamic conditions or inspired oxygen fraction and the interaction between these variables is unclear (15,41).

In trials, ANI showed significant changes between painful periods and non-painful periods in propofol anaesthetised patients, and was considered helpful to optimise remifentanyl administration (15). However, ANI did not perform as favourably in pain evaluation of awake patients in the immediate post-operative period, as the ability of ANI to distinguish between minor and severe pain yielded low sensitivity and specificity (41).

Many other factors, such as arousal, anxiety, agitation and noise, are known to increase sympathetic activity and are commonly encountered in the post-operative recovery room (41). This plethora of potential confounders in the post-operative recovery room setting is well described and is also suspected to impair the accuracy of other experimental monitors of nociception. The relationship between acute post-operative pain and the associated stress response may be far less linear than previously postulated, which would thus significantly influence the performance of any monitor for nociception which is based on the assessment of autonomic activity (41).

2.7.4 Pupillary Dilatation Reflex

The Pupillary Dilatation Reflex (PDR) is a sympathetic reflex that dilates the pupil in response to noxious stimuli (16). Pupil size is monitored and recorded using an infrared portable dynamic pupillometer following the application of a standardised painful stimulus. The pupillometer estimates the amplitude of the PDR, defined as the difference between the pupil size before and after stimulation, divided by the initial basal pupil size (16).

PDR has been assessed for the detection of pain and titration of analgesia in patients after surgery. The magnitude of PDR induced by a standard pressure stimulus adjacent to a surgical wound correlated with verbal pain ratings and the morphine requirements to obtain pain relief in the immediate post-operative period. However, no correlation was found between pain scores (whether patients were in pain or not) and basal pupil diameter in the absence of a noxious stimulus, suggesting that PDR only reflects changing levels of pain intensity and not constant pain. In addition, mechanisms for PDR are different in anaesthetised and unanaesthetised conditions, with the sympathetic component being predominant during the conscious state, resulting in less of a correlation with pain in anaesthetised patients (16).

This technique is limited by the concomitant use of drugs which alter pupillary diameter e.g. anti-cholinergics and dopaminergic receptor antagonists, ocular disease and ambient light. PDR measurement requires sophisticated equipment, inflicting of a noxious stimulus, patient co-operation and mobilisation and direct contact with patient's skin (15,16).

2.7.5 The difference between Response Entropy and State Entropy

In previous studies, it was found that remifentanyl titration guided by the difference between Response Entropy and State Entropy (RE-SE) during

general anaesthesia resulted in more stable haemodynamics, lower remifentanyl consumption and a clinically acceptable emergence time (35).

However, in subsequent evaluation of the variations of RE-SE during nociceptive stimulation, these findings were not supported (42). The evaluation of anaesthesia depth was good for RE; there was however no difference between RE and SE to predict analgesic requirement. Because RE includes muscular frequency analysis, it does not allow analgesic requirement evaluation in paralysed patients. Hence, RE-SE seems to be more related to the hypnotic state of the patient than the stress or pain component of the surgical trauma (34,42).

2.7.6 Near-Infrared Spectroscopy (NIRS)

Because physiological parameters remain relevant for many nonverbal patients in whom behavioural indicators can no longer be observed, research exploring innovative techniques is underway. NIRS is an available technology that has been used for the measurement of cortical responses to pain (9). Results from studies in critically ill infants and adult cardiac surgery patients have shown significant increases in cerebral oxygenation when patients were exposed to nociceptive stimuli. Also, the changes in cerebral oxygenation seem to be associated with the self-report of pain in adults (9).

2.7.7 Neuroimaging

Many new attempts at objectively measuring pain have focused on neurologic markers, attempting to encompass the large number of emotional, situational, and attentional factors that can modify the pain experience. The pursuit of a neuroimaging approach to measuring pain has intensified with better technology and increases in spatial and temporal resolution (27). Several brain regions show pain-related activations, and some degree of pain intensity encoding has been described. Methods such as magnetoencephalography, functional MRI, and positron emission tomography are used to explore the supraspinal neural correlates of pain. However, no neuroimaging technique has been established as a reliable method of measuring pain and the use of cumbersome equipment poses severe limitations in the operating theatre environment (27).

2.7.8 Stress hormones

Blood samples of patients under general anaesthesia have been analysed for levels of catecholamines as surrogates of stress (27,33). Rises in the concentration of epinephrine and norepinephrine were observed during stimulating events such as intubation and surgical skin incision. After the induction of anaesthesia and during anaesthesia without surgical stimulation, a fall in the levels of catecholamines was observed. These changes correlated positively with changes in heart rate, mean arterial pressure and skin conductance (33).

Although stress hormones are potential biomarkers of pain intensity, the process is costly, time consuming, not continuous and of questionable value in critically ill patients (27).

2.8 Pulmonary function under anaesthesia

The effects of general anaesthesia on pulmonary function are complex and relate to changes in patient positioning and loss of muscle tone, altered pulmonary mechanics owing to mechanical ventilation, as well as attenuation of respiratory drive by anaesthetic agents (44). Patient factors such as age, weight and gender are also known to affect respiratory function. Furthermore, stimulation of the sympathetic system by changes in fluid status, temperature and pain may also indirectly influence respiratory function (10,44).

The most important effect of anaesthetics on the control of breathing is a tendency to promote hypoventilation (10). The mechanism is probably due to depression of both the respiratory centre and intercostal muscle activity, with reduced sensitivity of the responses to CO₂ and hypoxia. The magnitude of hypoventilation is generally proportional to anaesthetic depth (10,44). These respiratory depressant effects may be antagonised by pain and surgical stimulation (10,45,46).

Volatile agents decrease tidal volume, but increase respiratory rate, thereby maintaining minute volume (45). Regardless of the agent used, light anaesthesia often results in irregular breathing patterns and breath holding.

Breaths become regular with deeper levels of anaesthesia (10). Isoflurane typically causes rapid, shallow breathing and even at low concentrations (less than 0.2 MAC) may blunt the normal response to hypoxia and hypercapnia. Sevoflurane depresses respiration to an extent similar to that of isoflurane. Volatiles (greater than twice MAC) severely blunt the response of increase in minute volume relating to increasing CO₂. Airway irritation is more common in children than adults, and is seen more often with rapid increases in inhaled agent concentration greater than one MAC (10,45).

Most induction agents inhibit the central ventilatory response to hypercarbia and hypoxia. Propofol is a profound respiratory depressant that usually causes apnoea following an induction dose. Propofol maintenance infusions typically result in a decrease in tidal volume and an increase in respiratory rate (10,45).

Opioids possess potent respiratory depressant properties (10,45). The CO₂ ventilatory response and hypoxic drive, which stimulate respiration, are significantly suppressed. This results in a decrease in tidal volume and respiratory rate. These effects are mediated through the respiratory centre in the brainstem. Opioids also affect the processing of pain, whereas volatiles and propofol do not have analgesic properties (47). The incidence of respiratory depression is also related to the type of opioid, total dose and route of administration (48).

Few studies have examined the respiratory response to skin incision during different anaesthetic techniques, yielding variable results (47). An increase in tidal volume without a change in frequency was observed during anaesthesia with enflurane. Propofol and opioid anaesthesia (alfentanil TCI), produced increases in minute ventilation but with considerable individual variation in the response. Both an increase in tidal volume and respiratory rate were observed, however, the authors concluded that the respiratory response is greatly influenced by choice and conduct of anaesthetic technique (47).

The literature reports a 0.1 to 3% incidence of adverse events attributed to opioid-induced respiratory depression (using variable criteria), with minor differences between different routes of administration (46,48,49). There has been a significant decrease in the incidence of respiratory depression over the course of 1980 to 1999, presumably due to increased use of combination analgesic strategies and improved monitoring (48). Although the majority of reported incidences of severe respiratory depression cited were successfully managed by the administration of naloxone and/or intervention by the anaesthesiologist, the potential for morbidity and even mortality still exists (50).

Controversy exists over the definition of respiratory depression and what constitutes an adverse respiratory event (46,48,49). A number of criteria have been used to define respiratory depression including:

1. hypoventilation (defined as respiratory rate less than eight to 12 breaths per minute {bpm}).

2. hypercarbia (defined as PaCO_2 greater than 6.5 kPa or greater than 50 mmHg).
3. oxygen desaturation (defined as saturation less than 85 to 90%).
4. requirement for naloxone.

Of these, respiratory rate (RR) is the most frequently used index of hypoventilation (38,48). A ventilatory frequency of less than 10 bpm is the commonest cut-off figure, although RR of less than eight bpm or less than 12 bpm are occasionally used. Frequently, ventilatory frequency is used in conjunction with pulse oximetry, but not all cases of respiratory depression have both low RR and low oxygen saturation, particularly when the patient is receiving supplemental oxygen (48). Oxygen saturation and breathing frequency are thus only surrogate indicators of ventilatory drive and provide limited information about the effects of a drug on the respiratory control system (50).

The occurrence of respiratory depression may be delayed (46,49). Pharmacokinetic-pharmacodynamic models of morphine suggest that maximum respiratory depression occurs at approximately one hour 40 minutes after a single intravenous dose and may persist for hours (46). In addition, patients with respiratory depression tend to tolerate an obstructed airway. Sleep and a quiet environment intensify the depressant effects of opioids (46,49). The occurrence of opioid-induced respiratory depression without concomitant reduction in breathing rate is also highlighted, with the

conclusion that RR is a very unreliable index of impaired respiratory drive (46).

Although mu-receptors are the key targets for both opioid-induced respiratory depression and anti-nociception, their effects are thought to occur independently (46,50). The recommended dose of morphine for an average adult is 0.14 to 0.2 mg/kg body weight. At this dose range, a theoretical therapeutic window exists where pain responses are reduced by 50 to 25% and respiration is simultaneously reduced by 50 to 40% of normal. Within this therapeutic window, the concentration-response curve is steeper for analgesia than for respiratory depression (46). Although RR may be considered an unreliable index of impaired respiratory sensitivity, it may still reflect pain status (50).

The potential for respiratory depression is commonly considered the most important adverse effect in the selection of analgesic technique (48). Opioid analgesics remain the most commonly used drugs in the treatment of moderate to severe post-operative pain. Thus the optimal balance between adequate analgesia and minimal respiratory depression is challenging to achieve (38,50). Furthermore, there are various patient groups who are at higher risk for respiratory depression and the risk is greater with increasing opioid doses. Proper identification of these patients and adequate post-operative monitoring are a prerequisite to provide appropriate pain relief and reduce adverse respiratory events (50).

In conclusion, the combined effects of anaesthetic techniques and surgical stimuli may cause unpredictable changes in minute ventilation (10,45). Monitoring RR in addition to other routinely monitored variables, may provide insight into pain status and respiratory adequacy.

2.9 Conclusion

Effective pain relief carries significant health and economic benefits to patients (13). Adequate assessment of pain, using validated tools appropriate to the population or individual, is an essential prerequisite of successful pain management (29).

Efficacious analgesic strategies are based on the accuracy of pain level evaluation at the time of patient emergence from anaesthesia (16). Current clinical anaesthetic practice comprises the titration of multimodal analgesics to variations in patient vital signs. Intra-operative changes in breathing rate and/or volume continue to be considered significant indicators of pain in spontaneously breathing anaesthetized patients, despite minimal formal investigation for correlation (14).

The accurate evaluation of intra-operative pain is therefore a key factor for successful post-operative pain relief (16,39). Owing to the paucity of methods of assessing intra-operative analgesic adequacy, there is a need for a technique that is simple to use, affordable, reliable and valid for the assessment of pain in patients under general anaesthesia until new anti-

nociceptive monitoring technologies are perfected and become incorporated into widespread clinical use.

Redefining successful pain management as a quality improvement measure requires a multifaceted and multidisciplinary approach (4,26). Although, improved assessment of intra-operative pain is only one element of this approach, it may provide a way forward in enhancing the caliber of post-operative pain management (2).

CHAPTER 3: METHODOLOGY

3.1 Introduction

This chapter provides an extensive description of the methodology used for the study.

3.2 Study design

This study is a prospective observational pilot study.

- Prospective:** The patients were followed forward in time until the required data was collected.
- Observational:** The data was collected without any intention of intervention in the surgical and anaesthetic management of the participants.
- Pilot:** A small-scale preliminary study was conducted in order to evaluate feasibility, time, cost, adverse events, and effect size in an attempt to predict an appropriate sample size and improve upon the study design prior to performance of a full-scale research project.

This study design was chosen because it provides an appropriate method to investigate the relationship between intra-operative respiratory rate and post-operative analgesic state. The methodology is in accordance with the international guidelines for observational studies (51).

3.3 Study site

The study was conducted in the general surgery theatres and post-operative recovery room in J.D. Allen theatre complex of CHBAH, in Soweto, Johannesburg. CHBAH is a central public hospital and contains 2 800 beds.

3.4 Study population

The study population consisted of adult female patients presenting for elective breast surgery.

3.5 Study period

Data collection was done over the period March 2011 to November 2012. The majority of data was collected May to November 2012.

3.6 Ethical considerations

This study was approved by the University of the Witwatersrand, Human Research Ethics Committee (**Appendix A**).

The study was approved by the Post-Graduate Committee of the University of the Witwatersrand, Faculty of Health Sciences (**Appendix B**).

The change of title of this study was approved by the Post-Graduate Committee of the University of the Witwatersrand (**Appendix C**).

Permission to conduct this study was granted by the Medical Advisory Committee at CHBAH (**Appendix D**).

This study has been structured in accordance with the principles outlined in the Declaration of Helsinki (11).

3.7 Notification of Department of Anaesthesia

Members of the Department of Anaesthesia at CHBAH were notified about the study prior to its commencement. Anaesthetists allocated to the elective breast surgery lists were made aware of which patients were study participants, and were requested to deliver a specific general anaesthetic technique, which is in accordance with routine practice but which would allow for standardisation. Anaesthetists not willing to be involved with the study were requested to contact the consultant responsible for list allocation.

3.8 Sample population and sampling method

In consultation with a biostatistician, a minimum sample size of 48 patients was calculated so as to find a coefficient of correlation (r) of 0.45, with 90% power and 95% confidence intervals. In order to allow for potential protocol violation, 60 patients were recruited, thus achieving 95% power with alpha equal to 0.001.

Consecutive convenience sampling was utilised to recruit study participants. The hospital runs four elective breast surgery slates per week, which are booked one day in advance. Patients meeting the selection criteria were identified and approached for the purposes of the study on the pre-operative day. The selection process stopped once 60 patients had been recruited.

3.9 Inclusion criteria

- Only patients from whom informed consent was obtained were included in the study.
- ASA 1 or 2 female patients aged between 18 and 60 years.
- Patients presenting for elective breast surgery during working hours from 08:00 to 16:00, Monday to Friday.

3.10 Exclusion criteria

- Patients with current respiratory or cardiac pathology.
- Patients with previous respiratory or cardiac pathology resulting in current functional limitation.
- Patients using medications known to affect respiratory function.
- Patients having received chemotherapy at any time in the past.
- Patients with chronic pain syndromes.
- Patients with a body mass index (BMI) in excess of 30.

- Patients with contra-indications to undergoing the standardised general anaesthesia study protocol.
- Patients with significant blood loss requiring more than one litre of fluid.
- Patients requiring naloxone for overdosing of morphine.

3.11 Data collection

Patients meeting the selection criteria were invited to participate in the study. The study aim and protocol were explained to them with the assistance of a translator where required. Patients received a printed document in English (**Appendix E**) detailing the purpose of the study, the nature of their involvement, the right to refuse to participate without repercussions to their care, as well as the right to withdraw from the study at any time. A 24-hour contact number was supplied should they require further information.

The researcher with the aid of a translator provided verbal information in a language that the patients could understand if they were not fluent in English, or were unable to read the document. Patients were requested to sign a consent document if they agreed to participate in the study (**Appendix F**). The study participants were then interviewed and educated about the Verbal Numeric Rating Scale (VNRS). Data was captured on the data collection sheet (**Appendix G**).

Patients' names and hospital numbers were kept separate from the data forms, and were encoded by a numerical coding system. This code remains known only to the investigator. All information that would link a patient's identity to the study was kept separate and confidential. Patients were allowed to withdraw from the study at any time and no patient was coerced to participate in the study.

3.11.1 Patient information

Data collected was entered onto a separate data sheet for each patient, and also onto a spreadsheet. The details of the collected data are as follows:

- Information regarding patient age, BMI, ASA classification, relevant past medical and surgical history, chronic medication, type of surgical procedure and baseline pain score (using VNRS) were collected at the pre-operative visit.
- Three measurements (made three minutes apart) of baseline respiratory rate, heart rate and non-invasive mean arterial blood pressure, with calculation of respective mean values were obtained pre-operatively.
- Types and dosages of analgesic drug(s) administered to the patient intra-operatively.
- Three measurements (made three minutes apart) of spontaneous respiratory rate, ETCO₂, heart rate and non-invasive mean arterial

blood pressure, with calculation of respective mean values were obtained at the end of the surgical procedure prior to emergence from anaesthesia.

- VNRS assessment after emergence from anaesthesia (VNRS1).
- Repeat VNRS assessment before discharge from the post-operative recovery room (VNRS2).
- Types and dosages of rescue analgesia (if required).
- Presence and management of side-effects.

3.11.2 Procedure in the operating theatre

The attending anaesthetist proceeded with the delivery of a standardised general anaesthesia protocol in every study participant. Initially, intravenous access was obtained in the patient and an infusion of one litre of Ringer's Lactate was commenced. Routine intra-operative monitors were applied to the patient, consisting of a non-invasive blood pressure (NIBP) cuff, pulse oximetry probe, electrocardiograph (ECG) leads, temperature probe, gas analyser, as well as end-tidal CO₂ (ETCO₂) capnograph (Delta Infinity[®]) which was also used as a monitor of respiratory rate. Three measurements (made three minutes apart) of respiratory rate, heart rate and non-invasive mean arterial blood pressure respectively were recorded by the principal investigator and mean baseline values for each parameter were calculated.

Standard elective sequence induction of anaesthesia included propofol titration to loss of eyelash reflex, and fentanyl one to two mcg/kg administered

intravenously. Next, a laryngeal mask airway (LMA) was inserted and the patient was kept breathing spontaneously or received assisted ventilation to maintain ETCO_2 within the limits of 30 to 55 mmHg until spontaneous ventilation resumed. Inspired fraction of O_2 (FiO_2) greater than 0.4 with a mixture of air was ensured. Anaesthesia was maintained with isoflurane or sevoflurane, titrated to achieve a minimum alveolar concentration (MAC) of 0.9 to 1.2. Fresh gas was delivered via a circle system, with no rebreathing. The attending anaesthetist controlled fluid administration and a central core temperature greater than 35°C was maintained.

The provision of analgesia was left to the discretion of the attending anaesthetist. Multimodal systemic analgesics were administered using a combination of fentanyl, morphine, paracetamol, diclofenac and/or ketamine. Sufficient time to allow for the titration of analgesics needed to be provided, thus a one hour minimum for the procedure was stipulated.

During wound closure and when the patient was breathing spontaneously, the principal investigator obtained three measurements (made three minutes apart) for respiratory rate, ETCO_2 , heart rate and non-invasive mean arterial blood pressure respectively. A mean value for each parameter was calculated. Volatile agents were discontinued at the end of the procedure and 100% O_2 was administered. The LMA was removed at the discretion of the attending anaesthetist. Patients were taken to the post-operative recovery room for routine post-operative care.

Upon arrival in the post-operative recovery room, when the patient was awake and able to verbalise, the patient was assessed for the presence of pain relating to the surgical site with a Verbal Numeric Rating Scale (VNRS). A VNRS assessment was repeated before discharge from the post-operative recovery room. This was to confirm that the patient had adequate relief from pain in the interim before the next dose of analgesia was received in the ward. Additional rescue analgesia was administered if required as indicated by a VNRS greater than three. Side-effects experienced by the patient were recorded and treated according to standard management protocols.

3.12 Validity and reliability

Validity and reliability of the study is ensured in the following manner:

- The inclusion and exclusion criteria allowed for the elimination of confounding factors that may otherwise influence a patient's respiratory rate or respiratory function.
- Anaesthesia was delivered by the anaesthetists allocated to the general surgery theatre lists, however, a predetermined standardised general anaesthetic protocol was followed.
- All data was collected by a single researcher, ensuring that the correct data was appropriately collected.
- The verbal numeric rating scale that was used for the assessment of pain by the principal investigator, has been validated as a pain assessment tool (1).

- The same capnograph (Delta Infinity[®]) was used to measure the respiratory rates of the study participants.
- Depth of anaesthesia was controlled for with the use of end-tidal gas analysis, thus eliminating awareness as a possible confounder.

3.13 Data analysis

Demographic, clinical and surgical data was entered on a Microsoft Excel[®] spreadsheet, and averages, frequencies and standard deviations were calculated. Analysis was performed using STATA[®] Version 12 Statistical Package.

A Spearman correlation coefficient (r) and coefficient of determination (r^2) were determined with linear regression. The threshold for statistical significance was set at p value less than 0.05.

The validity of respiratory rate as a predictor for post-operative pain was calculated using a non-parametric receiver-operating characteristic (ROC) curve without covariates. The ROC curve was built by plotting the sensitivity, or true positive rate, as a function of the false positive rate (100-specificity) at different respiratory rates. The software generated the respiratory rate with the highest sensitivity and specificity to conclude that a patient had moderate to severe pain (VNRS greater than three) and allowed for calculation of the Likelihood Ratio, as defined by the formula: $LR+ = \text{sensitivity} / (1 - \text{specificity})$.

3.14 Conclusion

This chapter provides an in-depth discussion of the methodology used in this study. The results obtained adhering to the study methodology are presented in the following chapter.

CHAPTER 4: RESULTS AND DISCUSSION

4.1 Introduction

In this chapter the results of the study are presented and discussed.

The following abbreviations are used in this chapter:

HIV = Human Immunodeficiency Virus

VSD = Ventricular septal defect

WLE = Wide local excision

ALND = Axillary lymph node dissection

SLNB = Sentinel lymph node biopsy

BBR = Bilateral breast reduction

4.2 Sample size and patient refusal

A total of 60 patients were approached to participate in the study. No patients refused to participate and there were no missing data.

4.3 Results relating to characteristics of study participants

4.3.1 Demographic characteristics

The demographic characteristics of the study participants are displayed in **Table 4.1**. None of the study participants had any baseline pain. 48 patients (80%) were classified as ASA 1 and 12 patients (20%) as ASA 2.

Table 4.1 Demographic characteristics of sample population

	n	Mean $\pm$ SD	Min	Max
Age (years)	60	38.58 $\pm$ 12.41	18	60
BMI (kg.m ⁻²)	60	24.12 $\pm$ 4.23	18	30
Baseline Pain (VNRS)	60	0	0	0

4.3.2 Clinical characteristics

The clinical characteristics of the study participants are displayed in **Table 4.2**. This table provides information relating to the study participants' past medical and surgical histories.

Table 4.2 Clinical characteristics of sample population

		n	(%)
Past medical history	Hypertension	12	20
	Type 2 Diabetes mellitus	2	3.33
	Epilepsy	1	1.67
	Previous pulmonary tuberculosis	4	6.67
	HIV positive	10	16.67
Past surgical history	Caesarian section	8	13.33
	Hysterectomy	6	10.00
	Mastectomy	2	3.33
	Breast lump excision	3	5.00
	Tonsillectomy	1	1.67
	VSD repair	1	1.67
	Lipoma excision	1	1.67

4.3.3 Surgical characteristics

The indications for surgery as well as the type of surgery undergone by the study participants are displayed in **Table 4.3**.

Table 4.3 Surgical characteristics of sample population

		n	(%)
Indication for surgery	Breast carcinoma	24	40.00
	Breast tumor (histology unknown)	6	10.00
	Phylloides tumour	3	5.00
	Fibroadenoma(s)	21	35.00
	Paget's disease	1	1.67
	Bloody nipple discharge	3	5.00
	Large breasts	2	3.33
Type of surgery	Mastectomy ± ALND/SLNB	17	28.33
	WLE ± ALND/SLNB	5	8.33
	Excision of fibroadenoma(s)	21	35.00
	Re-excision of margins	2	3.33
	Oncoplastic BBR ± SLNB	6	10.00
	BBR	2	3.33
	Excision of breast tumour (histology unknown)	3	5.00
	Microductectomy	4	6.67

4.3.4 Chronic medication

The types and frequency of chronic medication taken by the study participants are displayed in **Table 4.4**.

Table 4.4 Chronic medication taken by sample population

Chronic medication	n	(%)
Hydrochlorothiazide	10	16.67
Enalapril	6	10.00
Nifedipine	4	6.67
Spironolactone	1	1.67
Antiretrovirals	8	13.33
Metformin	2	3.33
Simvastatin	1	1.67
Carbamazepine	1	1.67
Phenytoin	1	1.67

4.3.5 Results of vital signs and VNRS

The results of study participants' vital signs at baseline and at wound closure, as well as post-operative VNRS assessment are displayed in **Table 4.5**.

Table 4.5 Values of vital signs and post-operative VNRS

		n	Mean $\pm$ SD	Min	Max
Baseline	Respiratory rate (breaths/min)	60	14.58 $\pm$ 2.26	10	22
	Heart rate (beats/min)	60	74.33 $\pm$ 9.90	59	98
	Mean arterial pressure (mmHg)	60	94.82 $\pm$ 10.89	78	130
At wound closure	Respiratory rate (breaths/min)	60	15.03 $\pm$ 4.20	9	25
	Heart rate (beats/min)	60	71.03 $\pm$ 11.30	53	106
	Mean arterial pressure (mmHg)	60	78.30 $\pm$ 12.62	59	121
	End-tidal CO ₂ (mmHg)	60	39.0 $\pm$ 4.97	31	54
Post-operative	VNRS1	60	1.60 $\pm$ 2.17	0	7
	VNRS2	60	0.51 $\pm$ 0.77	0	2

A VNRS less than three indicating mild pain was found in 44 patients (73.33%), whereas 16 patients (26.66%) scored VNRS greater than three, requiring additional analgesia. The distribution of intra-operative vital signs in study participants with none to mild pain (VNRS less than three) and those with moderate to severe pain (VNRS greater than three) is illustrated in **Table 4.6**.

Table 4.6 The distribution of intra-operative vital signs versus VNRS <3 and VNRS >3

		VNRS <3 (%)	VNRS >3 (%)
Respiratory rate (breaths/min)	9-12	22 (36.67)	1 (1.67)
	13-16	13 (21.67)	1 (1.67)
	17-20	7 (11.67)	11 (18.33)
	21-25	1 (1.67)	4 (6.67)
Heart rate (beats/min)	<65	15 (25.00)	7 (11.67)
	65-80	19 (31.67)	7 (11.67)
	80-100	7 (11.67)	3 (5.00)
	>100	2 (3.33)	0 (0)
Mean arterial pressure (mmHg)	<70	7 (11.67)	7 (11.67)
	70-90	32 (53.33)	5 (8.33)
	90-110	4 (6.67)	3 (5.00)
	>110	0 (0)	2 (3.33)

4.3.6 Results of analgesics administered intra-operatively

The types, frequency and dosages of analgesics received intra-operatively by the study participants are shown in **Table 4.7**. The patients received a multimodal combination of fentanyl, morphine, paracetamol (Perfalgan), diclofenac and/or ketamine.

Table 4.7 Analgesic drugs administered intra-operatively

	n	Mean dose	Min dose	Max dose
Fentanyl (mcg)	60	137.50	100	300
Morphine (mg)	60	6.77	4.5	15
Perfalgan (g)	50	1	1	1
Diclofenac (mg)	35	72.86	50	75
Ketamine (mg)	8	16.88	10	25

4.3.7 Results of rescue analgesics

The types, frequency and dosages of rescue analgesics received in the post-operative recovery room by the study participants are shown in **Table 4.8**. The analgesics the patients had received intra-operatively were taken into consideration when selecting the choice of rescue analgesia, which consisted of a combination of morphine, paracetamol (Perfalgan), diclofenac and/or ketamine. At the subsequent pain assessment all patients scored VNRS less than or equal to two.

Table 4.8 Drugs administered as rescue analgesia

	n	Mean dose	Min dose	Max dose
Morphine (mg)	10	3.25	2	6
Perfalgan (g)	3	1	1	1
Diclofenac (mg)	4	75	75	75
Ketamine (mg)	5	16	15	20

4.3.8 Results of the presence and management of side-effects

Two patients (3.33%) experienced post-operative nausea and vomiting. They were managed with prochlorperazine 12,5mg and metoclopramide 10mg intravenously respectively, following which their symptoms resolved.

4.4 Results related to the primary objective

The positively skewed distribution of initial pain intensity as assessed by VNRS measurement, plotted as a bar graph, is shown in **Figure 4.1**. The relationship between respiratory rates versus the first VNRS scores is illustrated by the curve, which depicts the mean respiratory rate in each category of VNRS score. The trend shows an increase in mean respiratory rate with increased VNRS score. The low numbers of patients in the upper VNRS score categories account for the outlying values creating a dip in the curve.

A Spearman correlation coefficient of 0.62 was calculated between the intra-operative respiratory rates and post-operative VNRS scores, with p value less than 0.001. This is indicative of a moderately good positive correlation. The coefficient of determination (r^2) valued at 0.38 means that 38% of the effect on respiratory rate can be attributed to pain.

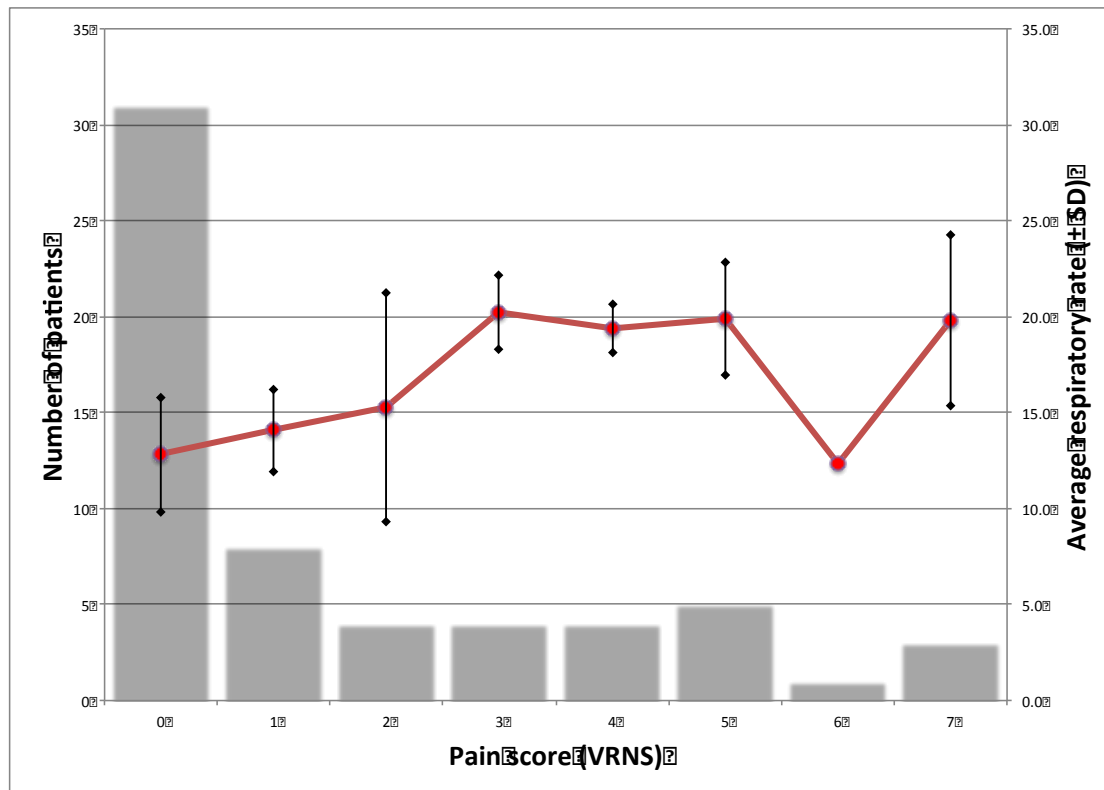


Figure 4.1 Correlation of respiratory rate and pain score (VNRS assessment). Respiratory rate is shown as median (circle on the curve) and 95% Confidence Intervals (represented by the vertical lines). Only one patient scored VNRS=6.

4.5 Results related to the secondary objective

A receiver-operating characteristic (ROC) curve was plotted to test the validity of respiratory rate as a predictor for post-operative pain, with a VNRS score more than three indicating unacceptable pain, requiring additional analgesia. (**Figure 4.2**). A moderate test characteristic was found with Area Under the Curve (AUC) of 0.77. The performance of a diagnostic test with a ROC curve AUC greater than or equal to 0.8 can be classified as good (15).

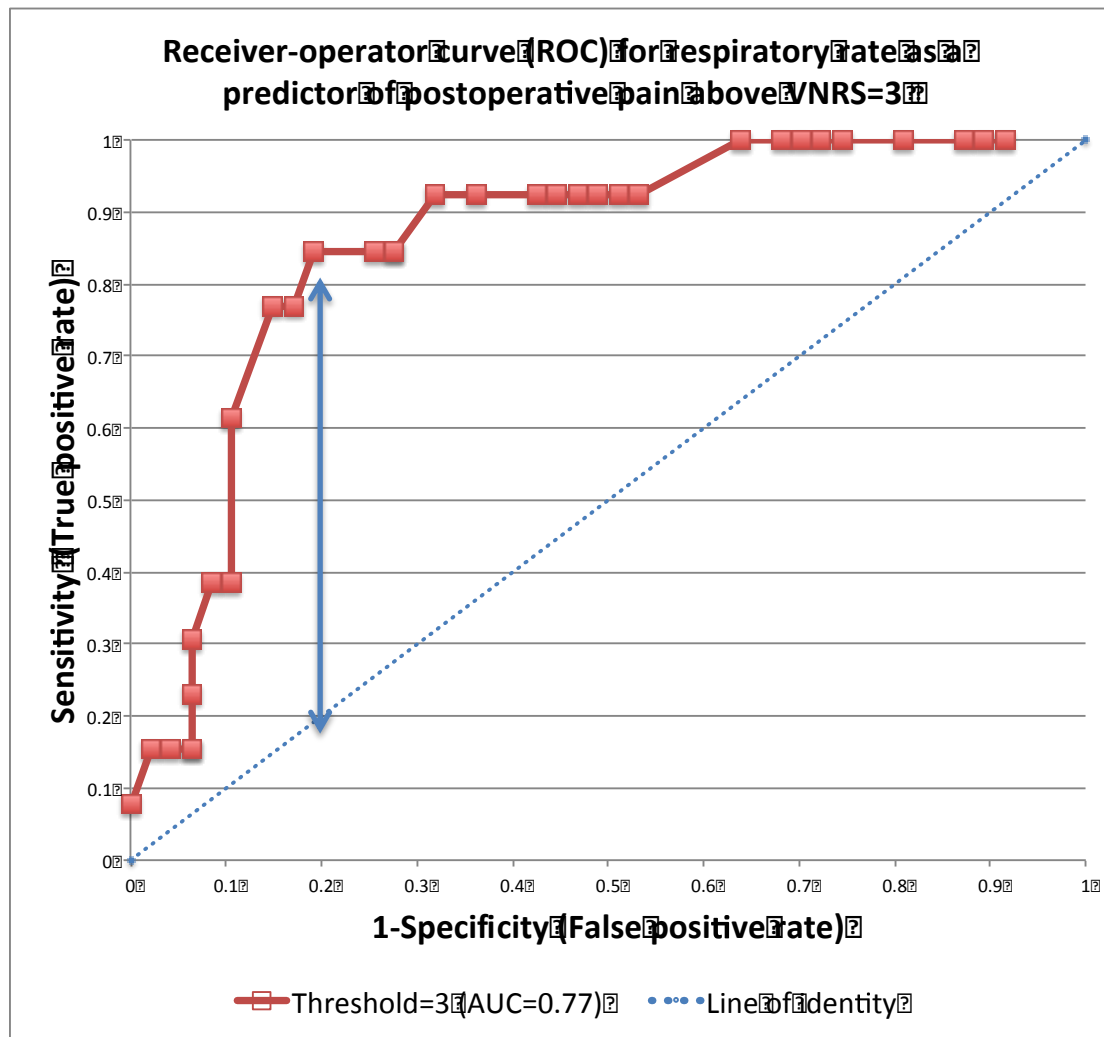


Figure 4.2 Receiver-operating characteristic (ROC) curve showing the relationship between sensitivity (true positive rate) and 100-specificity (false positive rate) in determining the value of the respiratory rate that predicts a VNRS of more than three, requiring additional analgesia.

The vertical line corresponding to the point furthest away from the Line of Identity, demonstrates the optimal discriminating function. Thus the suggested cut-off point for the respiratory rate with the optimal ratio of sensitivity and specificity to predict unacceptable pain at first measurement is more than or equal to 17 breaths per minute (bpm). The Likelihood Ratio was calculated at 3.31, therefore a respiratory rate of 17 bpm or more makes the patient 3.31 times more likely to have pain.

4.6 Summary of results

In summary, there exists a moderately good positive correlation between intra-operative respiratory rate in a spontaneously breathing patient under general anaesthesia, and post-operative pain as measured by the Verbal Numeric Rating Scale (VNRS).

The threshold intra-operative respiratory rate which best predicts post-operative pain (VNRS greater than three) is at a rate of 17 breaths per minute or more.

4.7 Discussion of results

4.7.1 Results relating to pain assessment scores

At the first pain assessment, 13 patients (21.67%) scored VNRS three to six (indicating moderate pain) and three patients (5%) scored VNRS greater than or equal to seven (indicating severe pain). This gives an overall incidence of 26.66% of post-operative pain, which corresponds to the lower end of the wide range of the incidence of post-operative pain of two to 70% as measured in previous trials (13-16).

This low incidence may be explained by the Hawthorne effect, where anaesthetists may have been more attentive to the delivery of analgesia as a result of participating in the study.

4.7.2 Results relating to the primary objective

A moderately good positive correlation (Spearman correlation coefficient, r equals 0.62) was found to exist between intra-operative respiratory rate and post-operative pain of increasing intensity. These findings may be explained by the activation of the sympathetic nervous system produced by pain, resulting in an increase in respiratory frequency. However, the coefficient of determination (r^2 equals 0.38) reveals that only 38% of the effect on respiratory rate can be attributed to pain, and that other factors of influence also need to be considered.

There were two patients who had a respiratory rate less than 17 breaths/min, but scored VNRS greater than three. This may be attributed to delayed recovery of perceptual cognitive function following general anaesthesia, morphine-induced side-effects such as sedation may increase the variability of pain perception, analgesics with amnestic properties might provide misleading results, patient misinterpretation of discomfort as pain or alternatively, drug-seeking behaviour in patients (16,30).

There were eight patients who had a respiratory rate greater than or equal to 17, but scored VNRS less than three. Factors to account for this may include anxiety, agitation, noise or other arousal of the sympathetic nervous system (16). Furthermore, patients may deny the presence of pain and refuse pain medications either because of fear of addiction or because any admission of pain is thought to be a sign of weakness (16). Once again patient misunderstanding of VNRS also needs to be considered.

4.7.3 Results relating to the secondary objective

With an AUC of 0.77 of ROC curve at the threshold of respiratory rate greater than or equal to 17 breaths per minute, the performance of intra-operative respiratory rate for the prediction of moderate to severe post-operative pain (VNRS greater than three) upon arrival in the post-operative recovery room may be classified as reasonably good.

The objective assessment of the immediate post-operative state of analgesia using Pupillary Dilatation Reflex (PDR) measurement and Analgesia Nociception Index (ANI) are currently under investigation (15,16,41). PDR measurement is partially invasive, as it requires direct contact with a patient's orbit as well as noxious stimulation prior to assessment. ANI allows for the continuous evaluation of pain both during surgery and in the non-communicative recovery phase, however, trial results have been inconsistent, with variable performance during different anaesthetic techniques. More trials would have to be performed before these modalities become validated for the use of pain assessment in the immediate post-operative period.

The use of intra-operative respiratory rate as a predictor for the adequacy of postoperative analgesia may offer advantages over PDR and ANI as this method precludes the need for sophisticated monitors, is completely non-invasive, affordable and easy to perform.

4.8 Conclusion

In this chapter the results of the study are presented and discussed. Demographic and clinical data are displayed as averages, frequencies and percentages. A Spearman correlation coefficient between the intra-operative respiratory rates and post-operative VNRS scores has been calculated, and a ROC curve was plotted to test the validity of respiratory rate as a predictor for post-operative pain.

The findings of the study have been analysed and interpreted, followed by a discussion of the issues raised by the results.

CHAPTER 5: SUMMARY AND CONCLUSIONS

5.1 Introduction

This chapter includes a summary and discussion of the study in terms of quality control and potential limitations, recommendations for further research and implications for clinical practice.

5.2 Summary of study

This study has shown that the efficacy of analgesia after breast surgery in female adults may be predicted intra-operatively from the respiratory rate if patients are allowed to breathe spontaneously. A respiratory rate of 17 breaths per minute or more may be associated with a high likelihood of post-operative pain as measured by a verbal numeric rating scale (VNRS), and therefore to require additional analgesia.

The use of intra-operative respiratory rate in the evaluation of pain may provide anaesthetists with a reliable, valid, objective, affordable and easy method of titrating analgesia intra-operatively and could offer an improvement on the current fragmented assessment of pain.

5.3 Limitations of study

- Patients were enrolled by consecutive convenience sampling. This method of sampling is not as robust as other methods, and may have introduced a potential for selection bias.
- The selected population with respect to study site, gender, comorbidities and type of surgery included in the current study represents only a small proportion of patients seen in daily clinical practice, so that these results cannot be extrapolated to all patients.
- The study is contextual with respect to one hospital and thus cannot be generalised to include other hospitals.
- Patient understanding of VNRS may have been inadequate resulting in post-operative discomfort and the presence of side-effects being misinterpreted as pain.
- The Hawthorne effect is likely to have occurred, where anaesthetists may have been more attentive to the delivery of analgesia as a result of participating in the study, resulting in a narrow distribution of respiratory rates as obtained from the study participants.
- The use of multiple attending anaesthetists caused a variation in analgesic strategies, however, this does reflect a real-life scenario.

5.4 Recommendations for further research

Since this was a pilot study, future studies can address the above-mentioned limitations by:

- A larger sample size.
- The inclusion of other surgical specialities and male patients.
- Performance of this study at multiple hospitals.
- More training of patients regarding the VNRS or the use of alternative pain assessment scales.
- The use of a standardised analgesia protocol.
- The use of a second investigator, who is blinded to the results of the respiratory rates, to measure the VNRS.
- The measurement of minute ventilation, to account for variations in tidal volume.
- To target an intra-operative respiratory rate less than 17 breaths per minute in a spontaneously breathing patient under general anaesthesia at the end of a surgical procedure, and measure pain after emergence from general anaesthesia.
- To conduct a follow-up interview with patients on the next post-operative day to determine their level of satisfaction with regards to the management of their post-operative pain and the factors contributing to it.

5.5 Conclusions of study

Accurate pain assessment is the cornerstone of successful pain management. No standardised technique currently exists for the evaluation of pain in patients under general anaesthesia, however, some evidence suggests that changes in respiration may reflect pain intensity.

This study has shown that measurement of intra-operative respiratory rate may provide a useful objective index of analgesia and may be recommended for use as an adjunct in the overall assessment of the adequacy of analgesia during the immediate post-operative period, as this has been shown to correlate with pain intensity.

The findings of this study grant anaesthetists an improved assessment of pain in resource-constrained environments, thus augmenting their management of post-operative analgesia. Improvement in post-operative pain relief may minimize patient complications and hospital costs, while concurrently enhancing patient comfort and satisfaction.

APPENDICES

Appendix A	Ethics approval certificate
Appendix B	Post-Graduate Committee approval certificate
Appendix C	Post-Graduate Committee approval of change of title
Appendix D	Permission from Medical Advisory Committee
Appendix E	Patient information sheet
Appendix F	Informed consent form
Appendix G	Data collection sheet

APPENDIX A: Ethics approval certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Magdalena Jaworska

CLEARANCE CERTIFICATE

M10962

PROJECT

indicator of post-operative analgesia.

The use of intra-operative respiratory rate as an

INVESTIGATORS

Dr Magdalena Jaworska.

DEPARTMENT

School of Clinical Medicine

DATE CONSIDERED

01/10/2010

DECISION OF THE COMMITTEE*

Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 01/10/2010

CHAIRPERSON


(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor: Dr Des Lines

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

APPENDIX B: Post-Graduate Committee approval certificate



Dr MA Jaworska
PO Box 521489
Saxonwold
2132
South Africa

Faculty of Health Sciences
Medical School, 7 York Road, Parktown, 2193
Fax: (011) 717-2119
Tel: (011) 717-2745

Reference: Ms Tania Van Leeve
E-mail: tania.vanleeve@wits.ac.za
11 October 2010
Person No: 384536
PAG

Dear Dr Jaworska

Master of Medicine (in the specialty Anaesthesia): Approval of Title

We have pleasure in advising that your proposal entitled "*The use of intra-operative respiratory rate as an indicator of the adequacy of post-operative analgesia*" has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

A handwritten signature in black ink, appearing to read "S. Benn", with a horizontal line underneath.

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

APPENDIX C: Post-Graduate Committee approval of change of title



Postgraduate Office, Faculty of Health Sciences
Wits Medical School, 7 York Road, PARKTOWN, 2193, Johannesburg • Tel: (011) 717 2000 • Fax: (011) 717 2119

APPLICATION FOR CHANGE OF TITLE OF APPROVED RESEARCH REPORT, DISSERTATION OR THESIS

Motivation / Reason for title change:

Clarification of type of study.

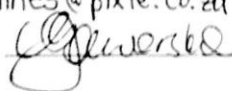
Recommendation of Department / School:

Approved.

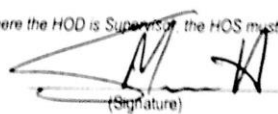
Student Surname and Initials: **M A Jaworska**
Student Number: **384 536**
Degree: **MMed (Anaesthesia)**
Department: **Anaesthesia**
Telephone: **0823712383**
E-mail: **madzia2908@gmail.com**

Previous Title: **The use of intra-operative respiratory rate as an indicator of the adequacy of post-operative analgesia.**
New Title: **A prospective observational study to determine the use of intra-operative respiratory rate as an indicator of the adequacy of post-operative analgesia – a pilot study.**

Supervisor/s: **Dr Desmond Lines**
Departments: **Anaesthesia**
Supervisor/s Telephone: **082 413 1512**
Supervisor/s E-mail: **lines@pixie.co.za**

Signatures of Student:  Supervisor: 

***HEAD OF DEPARTMENT / HEAD OF SCHOOL. *Where the HOD is Supervisor, the HOS must sign)**

MD Smith  **2/9/2013**
(Surname and Initials) (Signature) (Date)

DECISION OF CHAIR OF THE PG COMMITTEE: _____ **Signature:** _____
Date: _____

APPENDIX D: Permission from Medical Advisory Committee

MEDICAL ADVISORY COMMITTEE
CHRIS HANI BARAGWANATH HOSPITAL
PERMISSION TO CONDUCT RESEARCH

Date: 14 October 2010

TITLE OF PROJECT:

The use of intra-operative respiratory rate as an indicator of the adequacy of post-operative analgesia

UNIVERSITY: University

Principal Investigator: Dr M Jaworska

Department: Anaesthetics

Supervisor (If relevant): Dr D Lines

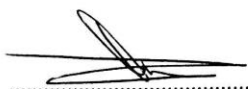
Permission Head Department (where research conducted) Yes

Date of start of proposed study: November

Date of completion of data collection: July 2011

The Medical Advisory Committee recommends/ ~~does not recommend~~ that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.



Recommended/ ~~Not Recommended~~

(On behalf of the MAC)

Date: 14/10/10

JOHN PETTIFOR
MBChB, FCP (S.A.)
CHIEF PAEDIATRICIAN



Approved/ ~~Not Approved~~

Hospital Management

Date: 19/10/2010

APPENDIX E: Patient information sheet

Hello, my name is Dr Megan Jaworska. I am a doctor at Chris Hani Baragwanath Hospital and I would like to invite you to take part in my study.

You are going to have an operation on your breast and will need anaesthesia medicine to make you sleep and control your pain during the operation. This is what we do for all patients that have this type of operation and the doctor giving the anaesthesia will do it in the same way for you. We have various ways of trying to make sure that patients don't wake up in pain and I am doing a study to find out another way. All I am going to do is monitor your breathing rate, heart rate and blood pressure at the end of the operation. When the operation is finished, you will be woken up and I will then check how well your pain is controlled with a pain scale. My study involves checking if there is a link between patients' breathing rate and the pain scale. If at any stage after the operation you are in pain, extra pain medicine will be given to you.

If you decide to take part in my study, then I will also ask you for some of your details, namely your age, weight, height, previous illnesses and operations, medicines that you are taking and type of breast procedure that you are going to have. All the information I get from you will be kept strictly confidential. The results of this study will help doctors improve their assessment and treatment of patients' pain during operations.

It is perfectly fine if you decide to be a part of the study, but want to pull out at a later stage. All your details will be removed from the study and the treatment that you receive at the hospital will not change in any way.

The Ethics Committee of Wits University has given permission for this study to be done. Professor Cleaton-Jones can be phoned on (011) 717 1234 to confirm this.

If you have any questions about this study, please contact me at time on 082 371 2383.

Thank you.

APPENDIX F: Informed consent form

I, _____, agree to take part in the study that Dr Jaworska has explained to me. I have read and understood the Information Sheet for Patients. All my questions have been answered. I understand that I will receive the same treatment whether I take part in the study or not. I am aware that all my details, including my participation in the study, will be kept strictly confidential. I understand that I am able to withdraw my participation at any time without any negative consequences to me. I am aware that Dr Jaworska is available for contact 24 hours a day at 082 371 2383.

Signed on _____ at _____

SIGNATURE

Study participant code: _____

APPENDIX G: Data collection sheet

- Study Participant number:
- Age:
- BMI:
- ASA classification:
- Relevant past medical and surgical history:
- Chronic medication:
- Type of surgical procedure:
- Baseline pain score:
- Baseline vital signs:

	Baseline-1 (Time 0)	Baseline-2 (Time0+3min)	Baseline-3 (Time0+6min)	Baseline-Mean
Respiratory rate				
Heart rate				
Mean arterial blood pressure				

- Total dose(s) of morphine and other analgesics administered:
- Intra-operative vital signs recorded during wound closure (GA = general anaesthesia):

	GA-1 (Time 0)	GA-2 (Time0+3min)	GA-3 (Time0+6min)	GA-Mean
Respiratory rate				
ETCO ₂				
Heart rate				
Mean arterial blood pressure				

- Post-operative verbal numeric rating scale (VNRS) score:

	VNRS-1	VNRS-2
VNRS score		

- Total dose of rescue analgesia administered:
- Presence and management of side-effects:

REFERENCES

1. South African Acute Pain Guidelines. South African Journal of Anaesthesia and Analgesia, 2009. 15 (6): 1-120.
2. White P, Kehlet H. Improving Post-operative Pain Management: What are the Unresolved Issues? Anaesthesiology, 2010. 112 (1): 220-225.
3. Ene KW, Nordberg G, Bergh I, Johansson FG, Sjostrom B. Post-operative pain management – The influence of surgical ward nurses. Journal of Clinical Nursing, 2008. 17: 2042-2050.
4. Stomberg M, Sjostrom B, Haljamae H. The role of the nurse anesthetist in the planning of post-operative pain management. American Association of Nurse Anesthetists Journal, 2003. 17 (3): 197-202.
5. Cade CH. Clinical tools for the assessment of pain in sedated critically ill adults. Nursing in Critical Care, 2008. 13 (6): 288-296.
6. Li D, Puntillo K, Miaskowski C. A Review of Objective Pain Measures for Use With Critical Care Adult Patients Unable to Self-Report. The Journal of Pain, 2008. 9 (1): 2-10.
7. Young J, Siffleet J, Nikoletti S, Shaw T. Use of a Behavioural Pain Scale to assess pain in ventilated, unconscious and/or sedated patients. Intensive and Critical Care Nursing, 2006. 22 (1): 32-39.
8. Gelinas C, Fillion L, Puntillo KA. Item selection and content validity of the Critical-Care Pain Observation Tool for non-verbal adults. Journal of Advanced Nursing, 2008. 65 (1): 203-216.
9. Arbour C, Gelinas C. Are vital signs valid indicators for the assessment of pain in post-operative cardiac surgery ICU adults? Intensive and Critical Care Nursing, 2010. 26 (2): 83-90.
10. Morgan G, Mikhail M, Murray M. Clinical Anesthesiology. 4th Edition. 2006, New York: Lange Medical Books / McGraw-Hill Medical Publishing Division.

11. World Medical Association. Declaration of Helsinki.
<http://www.wma.net/e/policy/b3.htm> (Accessed 31 May 2010).
12. Herr K, Coyne PJ, Manworren R, McCaffery M, Merkel S, Pelosi-Kelly J, et al.
Pain Assessment in the Non-verbal Patient: Position Statement with Clinical
Practice Recommendations. *Pain Management Nursing*, 2006. 7 (2): 44-52.
13. Moore RA, Straube S, Aldington D. Pain measures and cut-offs – no worse than
mild pain as a simple, universal outcome. *Anaesthesia*, 2013. 1-13.
14. Stomberg MW, Sjostrom B, Haljamae H. Routine intra-operative assessment of
pain and/or depth of anaesthesia by nurse anaesthetists in clinical practice.
Journal of Clinical Nursing, 2001. 10: 429-436.
15. Boselli E, Daniela-Ionescu M, Begou G, Bouvet L, Dabouz R, Magnin C et al.
Prospective observational study of the non-invasive assessment of immediate
post-operative pain using the analgesia/nociception index (ANI). *British Journal
of Anaesthesia*. Advance Access published April 16, 2013.
16. Aissou, M, Snauwaert A, Dupuis C, Atchabahian A, Aubrun F, Beaussier M.
Objective Assessment of the Immediate Post-operative Analgesia Using
Pupillary Reflex Measurement – A Prospective and Observational Study.
Anesthesiology, 2012. 116 (5): 1006-1012.
17. Li L, Liu X, Herr K. Post-operative Pain Intensity Assessment: A Comparison of
Four Scales in Chinese Adults. *Pain Medicine*, 2007. 8 (3): 223-234.
18. Jacobi J. et al. Clinical practice guidelines for the sustained use of sedatives and
analgesics in the critically ill adult. *Critical Care Medicine*, 2002. 30 (1): 119-141.
19. Storm H. Changes in skin conductance as a tool to monitor nociceptive
stimulation and pain. *Current Opinion in Anaesthesiology*, 2008. 21: 796-804.
20. Gerbershagen H, Rothaug J, Kalkman CJ, Meissner W. Determination of
moderate-to-severe post-operative pain on the numeric rating scale: a cut-off
point analysis applying four different methods. *British Journal of Anaesthesia*,
2011. 107 (4): 619-626.

21. Niraj G, Rowbotham DJ. Persistent post-operative pain: where are we now?
British Journal of Anaesthesia, 2011. 107 (1): 25-29.
22. Lamacraft G. The link between acute post-operative pain and chronic pain
syndromes. South African Journal of Anaesthesia and Analgesia, 2012. 18 (1):
45-50.
23. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating
scales. Journal of Clinical Nursing, 2005. 14: 798-804.
24. Carr ECJ, Thomas VJ. Anticipating and experiencing post-operative pain: the
patients' perspective. Journal of Clinical Nursing, 1997. 6: 191-201.
25. Hartrick CT, Kovan JP, Shapiro S. The Numeric Rating Scale for Clinical Pain
Measurement: A Ratio Measure? Pain Practice, 2003. 3 (4): 310-316.
26. Powell AE, Davies HTO, Bannister J, Macrae WA. Challenge of improving post-
operative pain management: case studies of three acute pain services in the UK
National Health Service. British Journal of Anaesthesia, 2009. 102 (6): 824-831.
27. Younger J, McCue R, Mackey S. Pain Outcomes: A Brief Review of Instruments
and Techniques. Current Pain and Headache Reports, 2009. 13 (1): 39-43.
28. Breivik EK, Bjornsson G, Skovlund E. A Comparison of Pain Rating Scales by
Sampling From Clinical Trial Data. Clinical Journal of Pain, 2000. 16 (1): 22-28.
29. Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstad L, Breivik
EK, et al. Assessment of pain. British Journal of Anaesthesia, 2008. 101 (1): 17-
24.
30. Liu WHD, Aitkenhead AR. Comparison of Contemporaneous and Retrospective
Assessment of Post-operative Pain using the Visual Analogue Scale. British
Journal of Anaesthesia, 1991. 67: 768-771.
31. Stomberg MW, Sjostrom B, Haljamae H. Assessing Pain Responses During
General Anaesthesia. American Association of Nurse Anesthetists Journal,
2001. 69 (3): 218-222.

32. Snejd JR. Depth-of-anaesthesia monitoring. *South African Journal of Anaesthesia and Analgesia*, 2012. 18 (1): 27-29.
33. Storm H, Myre K, Rostrup M, Stokland O, Lien MD, Raeder JC. Skin conductance correlates with peri-operative stress. *Acta Anaesthesiologica Scandinavica*, 2002. 46: 887-895.
34. Storm H, Shafiei M, Myre K, Raeder J. Palmar skin conductance compared to a developed stress score and to noxious and awakening stimuli on patients in anaesthesia. *Acta Anaesthesiologica Scandinavica*, 2005. 49: 798-803.
35. Chen X, Thee C, Gruenewald M, Whent J, Illies C, Hoecker J, et al. Comparison of Surgical Stress Index-guided Analgesia with Standard Clinical Practice during Routine General Anaesthesia: A Pilot Study. *Anaesthesiology*, 2010. 112 (5): 1175-1183.
36. Aubrun F, Hrazdilova O, Langeron O, Coriat P, Riou B. A high initial VAS score and sedation after iv morphine titration are associated with the need for rescue analgesia. *Canadian Journal of Anesthesia*, 2004. 51 (10): 969-974.
37. Hammoud HA, Simon N, Urien S, Riou B, Lechat P, Aubrun, F. Intravenous morphine titration in immediate post-operative pain management: Population kinetic-pharmacodynamic and logistic regression analysis. *Pain*, 2009. 144: 139-146.
38. Aubrun F, Mazoit JX, Riou B. Post-operative intravenous morphine titration. *British Journal of Anaesthesia*, 2012. 108 (2): 193-201.
39. Ledowski T, Bromilow, J, Wu M, Paech J, Storm H, Schug SA. The assessment of post-operative pain by monitoring skin conductance: results of a prospective study. *Anaesthesia*, 2007. 62: 989-993.
40. Ledowski T, Ang B, Schmarbeck T, Rhodes J. Monitoring of sympathetic tone to assess post-operative pain: skin conductance vs surgical stress index. *Anaesthesia*, 2009. 64: 727-731.

41. Ledowski T, Tiong WS, Lee C, Wong B, Fiori T, Parker N. Analgesia nociception index: evaluation as a new parameter for acute post-operative pain. *British Journal of Anaesthesia*. Advance Access published April 23, 2013.
42. Dierckens E, Fleyfel M, Robin E, Legrand A, Borel M, Gambier L, et al. Is entropy a monitor for the guidance of intraoperative analgesia? *Annales Francaises d'Anesthesie et de Reanimation*, 2007. 26: 113-118.
43. Logier R, Jeanne M, Tavernier B, de Jonckheere J. Pain/Analgesia evaluation using heart rate variability analysis. *EMBS Annual International Conference, Proceedings of the 28th IEEE. Engineering in Medicine and Biology Society*, 2006. 1: 4303-6.
44. Hedenstierna G. Chapter 15: Respiratory Physiology. In: Miller R, editor. *Miller's Anesthesia 7th Edition*. USA: Churchill Livingstone Elsevier. 2010, 771-846.
45. Milner A, Welch E, editors. *Applied Pharmacology in Anaesthesiology and Critical Care*. 2012, South Africa: Medpharm Publications.
46. Coetzee JF. Safety of pain control with morphine: new (and old) aspects of morphine pharmacokinetics and pharmacodynamics. *South African Journal of Anaesthesia and Analgesia*, 2010. 16 (2): 7-15.
47. Dockery MP, Drummond GB. Respiratory response to skin incision during anaesthesia with infusions of propofol and alfentanil. *British Journal of Anaesthesia*, 2002. 88 (5): 649-652.
48. Cashman JN, Dolin SJ. Respiratory and haemodynamic effects of acute post-operative pain management: evidence from published data. *British Journal of Anaesthesia*, 2004. 93 (2): 212-223.
49. Shapiro A, Zohar E, Zaslansky R, Shabat S, Fredman B. The frequency and timing of respiratory depression in 1524 post-operative patients treated with systemic or neuraxial morphine. *Journal of Clinical Anesthesia*, 2005. 17: 537-542.

50. Dahan A, Aarts L, Smith TW. Incidence, Reversal and Prevention of Opioid-induced Respiratory Depression. *Anesthesiology*, 2010. 112 (1): 226-238.
51. http://www.strobe-statement.org/fileadmin/strobe/uploads/checklists/STROBE_checklist_v4_combined.pdf (Accessed 10 March 2013).