THE AMOUNT OF MORPHINE ADMINISTERED PER PATIENT, FOR POSTOPERATIVE PAIN, USING A PATIENT-CONTROLLED ANALGESIA (PCA) DEVICE: AT UNIVERSITAS ACADEMIC HOSPITAL, BLOEMFONTEIN, FROM JANUARY 2015 TO DECEMBER 2017.

PRINCIPLE INVESTIGATOR:

Dr George Petrus Johannes Kotzé

MBChB(UFS); DA(SA); FCA(SA)

Registrar: Anaesthesia

Department of Anaesthesiology

University of the Free State

Bloemfontein

DECLARATION:

Submitted in fulfilment of the requirements in respect of the Master's Degree MMed in the Department of Anaesthesiology in the Faculty of Health Sciences at the University of the Free State.

SUBMISSION DATE:

4 December 2020

SUPERVISOR:

Professor Gillian Lamacraft

Associate Professor / Chief Specialist and Head of Pain Control Unit

Department of Anaesthesiology

University of the Free State

Bloemfontein

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DECLARATION OF AUTHORSHIP

I, George Petrus Johannes Kotzé, declare that the coursework Master's Degree mini-dissertation that I herewith submit in a publishable manuscript format for the Master's Degree qualification MMed at the University of the Free State is my independent work, and that I have not previously submitted it for a qualification at another institution of higher education.

ACKNOWLEDGEMENTS

The researcher would like to express his sincere gratitude to the following individuals:

Prof G Lamacraft for her guidance as study supervisor.

Dr EW Turton for his constant motivation to see the study through to completion.

Prof BJS Diedericks for his role as mentor and research input.

Prof G Joubert for her statistical input and timeously analysis of the data.

ABSTRACT

Background: Intravenous morphine patient-controlled analgesia (PCA) is one of the modalities used by anaesthesiologists to treat patients after operation for acute postoperative pain. About 50% of patients experience inadequate pain control post-surgery when treated with traditional intramuscular (IM) opioids prescribed *pro re nata* (PRN). Patient-controlled analgesia can also be used to treat patients with chronic pain conditions, advanced metastatic cancer, and in pregnant patients during normal vaginal delivery. The development of intravenous morphine patient-controlled analgesia has led to more effective management of acute postoperative pain, especially in older patients with more comorbid conditions, where a more controlled administration of opioid analgesia is preferred. Other modalities of pain management, like neuraxial and regional analgesia techniques also provide efficacious control of post-surgical pain versus morphine PCA. These techniques are sometimes difficult to perform and contraindicated in patients taking anticoagulation therapy or patients with preexisting neurological deficits. Intravenous morphine patient-controlled analgesia remains the gold standard for treating pain in these patients.

Objectives: The aim and primary objective of the study was to determine how many intravenous (IV) morphine is being used via intravenous morphine patient-controlled analgesia at Universitas Academic Hospital per patient over a 24-hour period and to determine the amount of morphine unused and discarded as wastage.

Methods: A retrospective study was conducted including all adult patients that underwent surgery and received intravenous morphine patient-controlled analgesia at Universitas Academic Hospital in Bloemfontein from 2015 to 2017. Data related to morphine PCA usage and presence of side-effects were collected from the PCA record form which is kept in the patient's file after discharge.

Results: A total of 155 patients who received intravenous morphine patient-controlled analgesia after surgery were included in the study. The median age were 55 years with 48.6% female patients and 51.4% male. The median total dosage of morphine received per patient was

22.75 mg over 24 hours. The median volume of morphine solution discarded per patient was 60 ml. Morphine PCA was mostly used for neurosurgical procedures (28.2%), followed by general surgery (20.8%), and orthopaedic surgery (16.1%). 86.9% of patients reported sufficient analgesia with intravenous morphine patient-controlled analgesia and 77.8% of patients did not require breakthrough pain medication. The intravenous morphine PCA device was used with insight by 76.5% of patients. Only 53.6% of the PCA record forms were assessed as correct and completely documented.

Conclusion: This study found that the average total dosage of morphine being used per patient receiving intravenous morphine patient-controlled analgesia was 22.75 mg over a 24-hour period. This is much less than the 90 mg morphine solution being used in the morphine PCA pump. A large volume of morphine gets discarded as wastage. We recommend reviewing the intravenous morphine PCA protocol of Universitas Academic Hospital to decrease unnecessary morphine wastage. Further research opportunities include a cost analysis study of intravenous morphine PCA usage per patient at Universitas Academic Hospital.

KEYWORDS

Analgesia

Intramuscular

Intravenous

Local anesthetics

Morphine

Opioids

Pain control

Pain pump

Patient-controlled analgesia

LIST OF ABBREVIATIONS

Abbreviation	Meaning
ACLS	Advanced cardiac life support
FSDoH	Free State Department of Health
HSREC	Health Sciences Research Ethics Committee
ICP	Intracranial pressure
IQR	Interquartile range
IM	Intramuscular
IV	Intravenous
LAST	Local anesthetic systemic toxicity
MEAC	Minimum effective analgesic concentration
MEC	Minimum effective concentration
MMed	Master's degree in medicine
PACU	Post-anaesthetic care unit
PCA	Patient-controlled analgesia
PRN	*Pro re nata*
SAJAA	Southern African Journal of Anaesthesia and Analgesia
SOP	Standard operating procedure
UFS	University of the Free State

LIST OF APPENDICES

CHAPTER 1 – LITERATURE REVIEW

INTRODUCTION AND HISTORY OF PATIENT-CONTROLLED ANALGESIA

Effective treatment of acute pain remains one of the biggest challenges posed to the anaesthetist. Despite modern advances in analgesic medications and different treatment modalities, undertreatment of acute pain is likely to continue even today. About 50% of patients experience inadequate pain control post-surgery when treated with traditional intramuscular (IM) opioids prescribed *pro re nata* (PRN).

Patient-controlled analgesia (PCA) has been described and experimentally used for relief of pain since 1971. In 1968, Sechzer evaluated the response to small intravenous (IV) opioid bolus doses administered by a nurse on patient demand. Sechzer[1] became the true pioneer of patient-controlled analgesia by developing PCA technologies and prototypic pain pump devices. The development of patient-controlled analgesia had the goal in mind to establish effective and efficient pain relief by allowing a patient to press a button, on the patient's own demand, whereafter a predetermined and set bolus dose of a medication with analgesic properties is then administered to the patient via a device with a microprocessor and a pump. The bolus dose of analgesic medication is delivered stat to the patient or it can be concurrent with a low-dose background infusion of the same medication. In 1976 the first commercially available patient-controlled analgesia pump became available for use in the healthcare industry.[2] The Cardiff Palliator was engineered and developed by the Welsh National School of Medicine.[3]

With new advances and development in the healthcare industry, patient-controlled analgesia can now be delivered via different routes of administration. These include intravenously through peripheral venous cannulas or central lines, epidural catheters, peripheral nerve catheters, and transdermal administration systems.[4,5]

Different drugs can be administered via patient-controlled analgesia. These include opioids like fentanyl and morphine, and local anesthetics like lidocaine and bupivacaine. Dissociative drugs like ketamine or other analgesics like tramadol can be used as alternatives or adjuncts.

Intravenous patient-controlled analgesia is one of the modalities used by anaesthesiologists to treat patients after operation for acute postoperative pain. Patient-controlled analgesia can also be used in certain instances to treat patients with chronic pain conditions. Another known use for patient-controlled analgesia is in the parturient patient during normal vaginal delivery.[6]

INDICATIONS FOR PATIENT-CONTROLLED ANALGESIA

THE FOLLOWING ARE INDICATIONS FOR THE USE OF PATIENT-CONTROLLED ANALGESIA:

- Patients that are unable to take per os medication or do not tolerate the side-effects of oral pain medication.

- To reduce the workload and stress on the nursing personnel taking care of postoperative patients, especially in resource constraint environments making use of skeleton staffing.

- More efficient and timeously administration of pain medication in situations where the patient's fluctuation of pain does not synchronize with a prescribed, predetermined dosing schedule of as-needed pain medication.

- Patients suffering from constant chronic pain conditions are also ideal candidates for patient-controlled analgesia. Examples of illnesses causing constant chronic pain include advanced metastatic cancer, complex regional pain syndromes, and patients suffering from phantom limb syndrome after limb amputation.[7]

- Patients who receive indwelling peripheral nerve or epidural catheters intra-operatively. Post-surgery, these patients can administer and titrate their own pain medication. This allows for superior pain control over scheduled administration and dosing by nursing personnel and increases the patients satisfactory experience. It also decreases the burden on the post-anaesthetic care unit (PACU) and the acute pain service unit.

CONTRAINDICATIONS FOR PATIENT-CONTROLLED ANALGESIA

Contraindications for the use of patient-controlled analgesia can be divided into absolute and relative contraindications.

THE FOLLOWING ARE ABSOLUTE CONTRAINDICATIONS FOR PATIENT-CONTROLLED ANALGESIA:

- Patients who do not understand the modality of patient-controlled analgesia and who show no insight into using the PCA device.

- Patients not giving consent for the placement and use of a patient-controlled analgesia catheter and device.

- Infection, burns, or trauma at the planned site of patient-controlled analgesia placement.

- Systemic infection, haemodynamic instability, and septic shock.

- Known allergic reaction to the specific analgesic medication to be used in the PCA device.

- Patients who present with preexisting neurological deficits at the area where an indwelling nerve catheter will be placed.

- Patients with increased intracranial pressure (ICP) precludes the placement and use of epidural catheter patient-controlled analgesia.

THE FOLLOWING ARE RELATIVE CONTRAINDICATIONS FOR PATIENT-CONTROLLED ANALGESIA:

- Patients suffering from obstructive sleep apnea.

- Patients with documented or diagnosed bleeding diathesis.

- Patients who are receiving antithrombotic or anticoagulation therapy.

- Patients with chronic renal failure.

PATIENT-CONTROLLED ANALGESIA EQUIPMENT

The administration of patient-controlled analgesia requires the use of a microprocessor pump to deliver the medication to the patient. To make safe use of a patient-controlled analgesia pump and decrease the associated complications to the patient, all pumps must have the following essential components:

1. A locking device.

2. A medication or syringe chamber.

3. A programmable computer with a microprocessor and a display screen.

4. A patient administration on-demand button.

The anaesthetist will prepare a predetermined concentration of a selected analgesic medication and draw it up into the syringe. The device will then be unlocked by a key or code and the loaded syringe with medication is put into the medication chamber. The syringe should be connected to a patient-controlled analgesia device administration set. The medication chamber will be closed and locked again to prevent tampering of the syringe and medication. The patient-controlled analgesia device will then be programmed according to the following parameters:

1. Initial loading dose.

2. PCA delivery dose.

3. Lockout time or interval.

4. Continuous background infusion rate.

5. One-hour and four-hour maximum medication delivery limits.

During the placement of an intravenous patient-controlled analgesia device, the administration set of the loaded syringe gets connected to a properly placed and running intravenous fluid line, taking precaution that both the PCA administration set and intravenous fluid line has been primed and all the air displaced from both lines to prevent inadvertent air embolism. The running intravenous fluid line is used to drive the analgesic medication intravenously when the patient presses the on-demand button of the patient-controlled analgesia device.

It is of paramount importance that every healthcare worker taking care of patients with patient-controlled analgesia devices, familiarizes themselves with the specific device that their institution is making use of and the specific protocols and standard operating procedure (SOP) for PCA administration at their institution.

MEDICATIONS USED FOR PATIENT-CONTROLLED ANALGESIA

A variety of medications can be used in patient-controlled analgesia with opioids and local anaesthetics the most often used. Opioids are used for intravenous patient-controlled analgesia. Local anesthetics are used in conjunction with opioids for patients with epidural catheter patient-controlled analgesia.

OPIOIDS

The use of opioids can be distinguished into pure Mu opioid receptor agonists, Mu opioid receptor agonist-antagonists, and partial Mu opioid receptor agonists.

Pure Mu opioid receptor agonists include morphine, fentanyl, hydromorphone, meperidine, sufentanil, alfentanil, and remifentanil. Mu opioid receptor agonist-antagonists include butorphanol, nalbuphine, and pentazocine. Partial Mu opioid receptor agonists include buprenorphine and dezocine.

Other medications with analgesic properties can be used together with opioid-based patient-controlled analgesia. These medications include ketamine, clonidine, ketorolac, lidocaine, droperidol, magnesium, and naloxone.[8] These medications are used in an attempt to improve pain control and reduce the opioid associated side-effects. The use of these additional medications in patient-controlled analgesia have shown varying efficacy in improving pain control and patient satisfaction.[9]

There is a large variety of opioid-based medications available on the market for use with patient-controlled analgesia. Morphine remains the gold standard opioid for use with intravenous patient-controlled analgesia.

Local Anesthetics

The local anesthetics being used in patient-controlled analgesia include bupivacaine, levobupivacaine, and ropivacaine. They act as sodium channel blockers and are mainly used for indwelling nerve catheter or epidural catheter patient-controlled analgesia.

Planning and Preparation for Patient-controlled Analgesia

Before the use and placement of an intravenous patient-controlled analgesia device, the patient needs to be thoroughly examined and assessed to determine the eligibility of the patient for patient-controlled analgesia. This examination and assessment usually take place during the pre-operative consultation with the patient before the planned surgical intervention. The patient needs to be evaluated over specific domains, which include cognition, opioid naivety, level of pain, level of sedation, and respiratory function.

The cognitive evaluation of the patient is necessary to determine if the patient has the mental capacity to understand and use the patient-controlled analgesia device with insight. Concepts pertaining to the function and use of the PCA device are explained to the patient. These include on-demand dosing, interval time, lockout time, and expected pain relief. Expected side-effects that the patient might experience are also explained during this pre-assessment consultation.

A history of previous and current use of analgesic medication will help the anaesthetist to decide if the patient is opioid naïve. This will help determine the dosing, titration, and programming of the patient-controlled analgesia device for the specific patient.

Pain, level of sedation, and respiratory function should be assessed beforehand to ascertain a baseline for the patient before commencement of using the PCA device. Pain is assessed by making use of the numerical pain rating scale. Respiratory function is assessed by examining the respiratory rate, depth, effort, and breath sounds of the patient. This is necessary to determine if the pain medication is causing respiratory depression, one of the side-effects of opioid analgesia. After commencement of the patient-controlled analgesia device, periodic assessments need to take place to determine if adjustments to the PCA device is necessary to achieve desired analgesic outcomes.

Technique and Delivery of Patient-Controlled Analgesia

The PCA device makes use of certain preset programmable variables as safety precaution with the aim the minimize harm to the patient and decrease the undesirable experience of side-effects.

The initial loading dose – This can be titrated to reach the minimum effective concentration (MEC) of the opioid medication being used. The minimum effective analgesic concentration (MEAC) is the smallest concentration at which the patient experiences relief of pain. The MEAC is the difference between experiencing severe pain or analgesia.[10]

The bolus or on-demand dose – This is the dose of medication administered to the patient every time the on-demand button of the patient-controlled analgesia device is pressed.

The lockout interval time – This is the time period which renders the patient-controlled analgesia device inactive after a bolus or on-demand dose was administered. During this period, no medication will be administered to the patient, even if the patient is pressing the on-demand button. This is a built-in safety mechanism in the PCA device microprocessor to prevent overdosing of the patient. The normal lockout interval time is normally eight minutes for the average adult patient receiving intravenous morphine patient-controlled analgesia.

The continuous infusion rate – A background continuous infusion rate can be programmed separately form the on-demand dosing. This is used to maintain the minimum effective concentration of the chosen medication.

The four-hour maximum limit – This parameter limits the amount of medication administered to a patient within a four-hour period, independent of the total on-demands pressed by the patient. When the four-hour maximum set dose is reached, no further medication will be administered to the patient. This is an added safety mechanism to prevent overdosing of the patient. It can be used as an indicator of adequate pain control of the medication used and to adjust the preset dosing parameters if needed.[11]

Effective opioid analgesia can be achieved by optimizing the above-mentioned parameters. Individualize and titrate the dosage for each patient to achieve and maintain their minimum effective analgesic concentration. Constant plasma opioid concentrations should be maintained while trying to minimize or avoid fluctuations in peak and through levels.[12] The above cannot be achieved with PRN intramuscular opioid injections and the patient-controlled paradigm demonstrates superiority over intramuscular opioid injections.

To date, there are a multitude of different patient-controlled analgesia dosing strategies. This include different medications to be used and different settings for all the above mentioned PCA device parameters. Each Pain Control Unit should make use of their own dosing strategy with which they are familiar and make use of the approved patient-controlled analgesia protocols and SOP at their institution.

COMPLICATIONS OF PATIENT-CONTROLLED ANALGESIA

Complications related to the use of patient-controlled analgesia can broadly be distinguished into two groups. Complications that arise from the medication being used and complications inherent to the patient-controlled analgesia device or pump itself.

Run-away pumps – This is when there is malfunction of a pump. It is a mechanical error inherent to the pump and the device will deliver medication doses at incorrect amounts and intervals. Although mechanical failure of a pump is rare, this type of error can cause a potentially fatal overdose. It is essential to do periodic assessments of the patient for signs and symptoms of overdose and the PCA pump for mechanical malfunction and failure. Institutions should ensure maintenance of patient-controlled analgesia devices by adhering to regular service schedules.

Failure to use anti-reflux valves – These valves are necessary to prevent upstream flow of the opioid medication into the intravenous fluid line instead of intravenously into the circulatory system of the patient. Absence of anti-reflux valves will lead to opioid medication flowing upstream into the intravenous fluid infusion administration set. When the intravenous fluid line is subsequently flushed, this large dose of opioid medication will be delivered to the patient as a large bolus dose and can result in respiratory depression and overdose.

Incorrect syringe placement or damage to the syringe – If there is damage to the syringe or the syringe is placed incorrectly into the syringe chamber of the patient-controlled analgesia device, the content of the syringe can drain by gravity into the intravenous infusion line and be administered to the patient as a very large bolus dose. Patient-controlled analgesia administration sets should always be cross-clamped when changing a syringe or refilling an empty syringe. The PCA device should also be kept level to or below the level of entry of the intravenous infusion line into the patient. New and high-end patient-controlled analgesia devices have anti-siphon valves to prevent this complication form happening.

Patient-controlled analgesia by proxy – This phenomenon takes place when a person other than the patient is pressing the on-demand button to deliver a dose of pain medication to the patient. The person pressing the on-demand button thinks the patient is in pain and needs more analgesia. This can lead to unwanted side-effects and respiratory depression of the patient. To mitigate this from happening, only the patient should be allowed to press the on-demand button to deliver a dose of medication. Information and education should be given to

the patient, any visitors, and health care providers. This act is prohibited and dangerous to the patient.[13]

Patient-controlled analgesia device tampering – PCA devices should routinely be inspected for any signs of tampering or damage caused due to tampering. Only authorized personnel should have access to the syringe chamber, medication, and programming of the patient-controlled analgesia device computer. These personnel include the anaesthetist prescribing the patient-controlled analgesia device, the Acute Pain Service nurse taking care of the patient and the PCA device, and the Pain Control Unit specialist looking after the patient during the postoperative period. Only these authorized personnel should have access to the key or code for unlocking of the PCA device pump.

Side-effects of Patient-controlled Analgesia

Side-effects are mainly related to the choice of medication being used in the patient-controlled analgesia device. The most frequent side-effects occurring include nausea and vomiting, constipation, urinary retention, respiratory depression, pruritus, and allergic reactions. When local anesthetics are being used, the anaesthetist should also be observant for signs and symptoms of local anesthetic systemic toxicity (LAST).[14] Mild side-effects can be treated symptomatically as tolerated by the patient. In emergency situations where side-effects are eminently life threatening, resuscitation measures should be implemented immediately according to Advanced Cardiac Life Support (ACLS) guidelines.

The greatest risk for the development of hypoventilation and the occurrence of nocturnal hypoxemia is within the first twenty-four to forty-eight hours after surgery. The nursing personnel taking care of postoperative patients should frequently and carefully evaluate these patients to assess their level of pain, sedation, and respiratory function. When the patient-controlled analgesia device is used with insight, the total number of demands can be used to assess the opioid requirements of the patient. The PCA device parameters can then be adjusted accordingly if deemed necessary.

Clinical Significance and Enhancing Patient Outcome through Education

The modality of patient-controlled analgesia has proven effective for the use of acute, chronic, and postoperative pain. Patients experience higher rates of satisfaction from the use of patient-controlled analgesia over non-patient controlled opioid injections. This allows patients to have more control over their own pain and empowers them to take control over their care and recovery process. Nursing personnel also prefer the use of patient-controlled analgesia, as it reduces the stress on their daily workload.

Efficient use of patient-controlled analgesia as a pain control modality, requires a competent and dedicated multidisciplinary healthcare team. It is therefore of paramount importance that the healthcare team receives continuous education regarding the different routes of administration, variety of medications, dosing regimens, side-effects, and complications of patient-controlled analgesia. The healthcare team should be familiar and comfortable with evaluation and periodic assessment of patients receiving patient-controlled analgesia. Meticulous attention should be paid to the preparation of medication for use the pump and correct programming of the PCA device to prevent inadvertent drug errors and adverse outcomes from happening.

When comparing intravenous patient-controlled analgesia with traditional opioid injections, studies found no difference in the average length of hospital stay or significant difference between opioid related side-effects.[15] There is no clear answer regarding the cost-effectiveness of patient-controlled analgesia over traditional dosing, with studies giving different results.[16]

Summary and Conclusion

By convention patient-controlled analgesia (PCA) implies administration of intravenous opioids by voluntary patient control, in an on-demand, intermittent fashion. This can be done with or without a continuous background infusion of opioids as programmed on the infusion pump. When the patient experiences pain and pushes the on-demand button, a pre-programmed

dose of intravenous opioids is administered to the patient via a microprocessor-controlled infusion pump.[10]

This modality of analgesia delivery provides effective pain control, fewer side-effects, and acceptable patient satisfaction when compared with nurse-administered parenteral opioid administration.[17,18]

Other treatment modalities for postoperative pain have also proven to be as effective or even superior to intravenous patient-controlled analgesia use. A meta-analysis found that epidural analgesia, when compared with intravenous patient-controlled analgesia, provided superior post-operative pain relief. This was found to be true for all types of surgery for which epidural anaesthesia and analgesia could be performed.[19]

The use of intravenous opioid patient-controlled analgesia is not without side-effects. The most common side-effects being nausea and vomiting, pruritus, sedation and confusion, and respiratory depression.[20]

There are several factors that play a role in the use of patient-controlled analgesia. Patient characteristics such as age, gender, weight, opioid tolerance, chronic pain, and patient understanding, all influence patient-controlled analgesia use.[10]

Is intravenous patient-controlled analgesia cost-effective versus intramuscular analgesia? Conclusive data is lacking, and further all-encompassing cost analysis studies still need to be performed regarding the cost-effectiveness of intravenous patient-controlled analgesia compared to intermittent, nurse administered IM morphine. A study done by Colwell and Morris[21] in 1995, found that intravenous patient-controlled analgesia usage was more than twice as expensive as intramuscular injections for patients undergoing elective arthroplasty surgery.

AIMS AND OBJECTIVES OF THE RESEARCH TOPIC

At Universitas Academic Hospital in Bloemfontein, intravenous morphine patient-controlled analgesia is frequently used for gynaecological, general, orthopaedic, and neurosurgical operations. A standardized protocol regimen is used which comprises a solution of intravenous morphine 90 mg diluted up to 90 ml with sterile water for injection. The PCA infusion pump (IVAC PCAM by Cardinal Health) is pre-programmed to deliver a bolus of 1.0 – 1.5 mg morphine every time the on-demand button is pressed. Safety mechanisms which are also programmed into the microprocessor include a lockout time of 8 minutes and a 4-hourly maximum delivery of 15 – 20 mg morphine. Patients also receive paracetamol and tramadol when breakthrough pain is experienced.

It has been observed at Universitas Hospital that some patients use intravenous morphine patient-controlled analgesia to a greater extent than others. This has led to wastage of morphine left in the medication syringe of the patient-controlled analgesia device when it is routinely discontinued after 24 hours of use.

The aim of the research topic is to determine the amount of intravenous morphine that is being used per patient via intravenous morphine PCA over a 24-hour period at Universitas Academic Hospital in Bloemfontein. The researcher is not aware of any similar studies that has been done in South Africa at the time of writing.

The objective of the study will be to determine how much morphine is required to be drawn up per 24 hours for intravenous patient-controlled analgesia, so less morphine will be wasted. This will help us decide if the standard intravenous morphine patient-controlled analgesia protocol should be modified and encourage further research on patient-controlled analgesia at Universitas Academic Hospital.

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CHAPTER 2 - MANUSCRIPT

This manuscript is intended for publication in the Southern African Journal of Anaesthesia and Analgesia (SAJAA).

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GPJ Kotzé[1], G Lamacraft[1], G Joubert[2]

[1]Department of Anaesthesiology, Faculty of Health Sciences, University of the Free State, South Africa

[2]Department of Biostatistics, Faculty of Health Sciences, University of the Free State, South Africa

Corresponding author GPJ Kotzé, email: geonkot@gmail.com

ABSTRACT

Background: Intravenous patient-controlled analgesia (PCA) is one of the modalities used by anaesthesiologists to treat patients after operation for acute postoperative pain. About 50% of patients experience inadequate pain control post-surgery when treated with traditional intramuscular (IM) opioids prescribed *pro re nata* (PRN).

Methods: A retrospective study was conducted including all adult patients that underwent surgery and received intravenous morphine patient-controlled analgesia at Universitas Academic Hospital from 2015 to 2017. Data related to morphine PCA usage and presence of side-effects were collected from the PCA record form which is kept in the patient's file after discharge.

Results: A total of 155 patients who received intravenous morphine patient-controlled analgesia after surgery was included in the study. The median age were 55 years with 48.6% female patients and 51.4% male. The median total dosage of morphine received per patient was 22.75 mg over 24 hours. The median volume of morphine solution discarded per patient was 60 ml. Morphine PCA was mostly used for neurosurgical procedures (28.2%), followed by general surgery (20.8%), and orthopaedic surgery (16.1%). 86.9% of patients reported sufficient analgesia with intravenous morphine PCA use and 77.8% of patients did not require any breakthrough pain medication.

Conclusion: This study found that the average total dosage of morphine being used per patient receiving intravenous morphine patient-controlled analgesia was 22.75 mg over a 24-hour period. This is much less than the 90 mg morphine solution being used in the morphine PCA pump. A large volume of morphine gets discarded as wastage. We recommend reviewing the intravenous morphine PCA protocol of Universitas Academic Hospital to decrease unnecessary morphine wastage. Further research opportunities include a cost analysis study of intravenous morphine PCA usage per patient at Universitas Academic Hospital.

Keywords: analgesia, intravenous, intramuscular, local anesthetics, morphine, opioids, pain control, pain pump, patient-controlled analgesia

INTRODUCTION

Effective treatment of acute pain remains one of the biggest challenges posed to the anaesthetist. Despite modern advances in analgesic medications and different treatment modalities, undertreatment of acute pain is likely to continue even today. About 50% of patients experience inadequate pain control post-surgery when treated with traditional intramuscular (IM) opioids prescribed *pro re nata* (PRN).

Patient-controlled analgesia (PCA) has been described and experimentally used for relief of pain since 1971. Sechzer[1] became the true pioneer of patient-controlled analgesia by developing PCA technologies and prototypic machine devices. The development of patient-controlled analgesia had the goal in mind to establish effective and efficient pain relief by allowing a patient to press a button, on the patient's own demand, whereafter a predetermined bolus dose of a medication with analgesic properties is then administered to the patient via a device with a microprocessor and a pump. The bolus dose of analgesic medication is delivered stat to the patient or it can be concurrent with a low-dose background infusion of the same medication. In 1976 the first commercially available patient-controlled analgesia pump became available for use in the healthcare industry.[2] The Cardiff Palliator was engineered and developed by the Welsh National School of Medicine.[3]

With new advances and developments in the healthcare industry, patient-controlled analgesia can now be delivered via different routes of administration. These include intravenously (IV) through peripheral venous cannulas or central lines, epidural catheters, peripheral nerve catheters, and transdermal administration systems.[4,5]

Intravenous morphine patient-controlled analgesia is one of the modalities used by anaesthesiologists to treat patients after operation for acute postoperative pain. Another known use for patient-controlled analgesia is in the parturient patient during normal vaginal delivery.[6] Patient-controlled analgesia can also be used in certain instances to treat patients with chronic pain conditions like advanced metastatic cancer, complex regional pain syndromes, and phantom limb syndrome.[7]

The administration of patient-controlled analgesia requires the use of a microprocessor pump to deliver the medication to the patient. To make use of a patient-controlled analgesia pump safe and decrease the associated complications to the patient, all pumps must have the

following essential components: a locking device, syringe chamber, a programmable microprocessor computer with a display screen, and a patient administration on-demand button.

A predetermined concentration of a selected analgesic medication is drawn up into a specific syringe. The device is unlocked by a key or code and the syringe with medication loaded into the medication chamber of the device. The medication syringe gets connected to a patient-controlled analgesia device administration set. The medication chamber is then closed and locked again to prevent tampering of the syringe and medication. The patient-controlled analgesia device is then programmed according to the following parameters: initial loading dose, PCA delivery dose, lockout time interval, continuous background infusion rate, one-hour, and four-hour maximum medication delivery limits.

The initial loading dose is titrated to reach the minimum effective concentration (MEC) of the opioid medication being used. The minimum effective analgesic concentration (MEAC) is the smallest concentration at which the patient experiences relief of pain. The minimum effective analgesic concentration is the difference between the patient experiencing severe pain or analgesia.[8]

The four-hour maximum parameter limits the amount of medication administered to a patient within a four-hour period, independent of how many times the on-demand button is pressed. When the limit is reached, no further medication will be administered to the patient. This can be used as an indicator of adequate pain control of the medication used and to adjust the preset dosing parameters if needed.[9] Constant plasma opioid concentrations should be maintained while trying to minimize or avoid fluctuations in peak and through levels.[10] The above cannot be achieved with PRN intramuscular opioid injections and the patient-controlled analgesia paradigm demonstrates superiority over intramuscular opioid injections.

During the placement of an intravenous patient-controlled analgesia device, the administration set of the loaded syringe gets connected to a properly placed and running intravenous fluid line, taking precaution that both the PCA administration set and intravenous fluid line have been primed and all the air displaced from both lines to prevent an air embolism.

It is of paramount importance that every healthcare worker taking care of patients with PCA devices, familiarizes themselves with the specific device or pump that is used by their institution and the protocols and standard operating procedure (SOP) for patient-controlled analgesia.

A variety of medications can be used in patient-controlled analgesia, with opioids and local anaesthetics the most often used. Opioids are used for intravenous patient-controlled analgesia. Pure Mu opioid receptor agonists include morphine, fentanyl, hydromorphone, meperidine, sufentanil, alfentanil, and remifentanil. Mu opioid receptor agonist-antagonists include butorphanol, nalbuphine, and pentazocine. Partial Mu opioid receptor agonists include buprenorphine and dezocine.

Other medications with analgesic properties like ketamine, clonidine, ketorolac, lidocaine, droperidol, magnesium, and naloxone can be used together with opioid-based patient-controlled analgesia.[11] The use of these additional medications in patient-controlled analgesia have shown varying efficacy in improving pain control and patient satisfaction.[12] Morphine remains the gold standard opioid for use with intravenous patient-controlled analgesia.

Before the use and placement of an intravenous patient-controlled analgesia device, the patient needs to be thoroughly examined and assessed to determine the eligibility of the patient to use patient-controlled analgesia. This examination and assessment usually take place during the pre-operative consultation with the patient before the planned surgical intervention. The patient needs to be evaluated over specific domains, which include cognition, opioid naivety, level of pain, level of sedation, and respiratory function.[8]

Complications related to PCA use can broadly be distinguished into two groups. Complications that arise from the medication being used and those that arise from the PCA device or pump itself, like run-away pumps, failure to use anti-reflux valves, incorrect syringe placement or damage to the syringe, PCA by proxy, and device tampering.[13]

Side-effects are mainly related to the choice of medication being used in the patient-controlled analgesia device. The most frequent side-effects occurring include nausea and vomiting, constipation, urinary retention, respiratory depression, pruritus, and allergic reactions.[14] When local anesthetics are used, the anaesthetist should also be observant for signs and symptoms of local anesthetic systemic toxicity (LAST).[15] Mild side-effects can be treated symptomatically as tolerated by the patient. In situations where side-effects are life threatening, resuscitation measures should be implemented immediately.

When comparing patient-controlled analgesia with traditional opioid injections, studies found no difference in the average length of hospital stay or significant difference between opioid related side-effects.[16] There is no clear answer regarding the cost-effectiveness of patient-controlled analgesia over traditional dosing with studies giving different results.[17] This

modality of analgesia delivery provides effective pain control, fewer side effects, and acceptable patient satisfaction when compared with nurse-administered parenteral opioid administration.[18,19] Other treatment modalities for postoperative pain have also proved to be as effective or even superior to intravenous patient-controlled analgesia use. A meta-analysis found that epidural analgesia when compared with intravenous patient-controlled analgesia provided superior post-operative pain relief. This was found to be true for all types of surgery for which epidural anaesthesia and analgesia could be performed.[20]

Is intravenous patient-controlled analgesia cost-effective versus intramuscular (IM) analgesia? Conclusive data regarding cost-effectiveness of PCA use is lacking and further all-encompassing cost analysis studies still need to be performed.[8] A study done by Colwell and Morris[21] in 1995 found that intravenous patient-controlled analgesia usage was more than twice as expensive as intramuscular injections for patients undergoing elective arthroplasty surgery.

At Universitas Academic Hospital intravenous morphine patient-controlled analgesia is frequently used for different surgical modalities. A standardized protocol regimen is used which comprises of a solution of intravenous morphine 90 mg diluted up to 90 ml with sterile water for injection. The infusion pump is pre-programmed to deliver a bolus of 1.0 – 1.5 mg morphine every time the on-demand button is pressed. Safety mechanisms which are also programmed into the microprocessor include a lockout time of 8 minutes and a 4-hourly maximum delivery limit of 15 – 20 mg morphine. The patients also receive paracetamol and tramadol during episodes of breakthrough pain. Some patients use patient-controlled analgesia to a greater extent than others. This has led to wastage of the morphine left in the syringe of the PCA device when it is routinely discontinued after 24 hours.

The aim and primary objective of the study was to determine how much intravenous morphine was used per patient via patient-controlled analgesia at Universitas Academic Hospital over a 24-hour period and to determine the amount of morphine discarded as wastage.

METHODS

A retrospective study was conducted including all adult patients that underwent surgery and received intravenous morphine patient-controlled analgesia at Universitas Academic Hospital in Bloemfontein from 2015 to 2017. Data related to morphine PCA usage and presence of side-

effects were collected from the PCA record form which is kept in the patient's file after discharge. The sample size was estimated to be approximately 50 – 100 patients.

It is standard practice that for every patient receiving intravenous patient-controlled analgesia, an accompanying form is completed (see Appendix E). This form is completed by the anaesthetist in theatre, the anaesthetic registrar at the Pain Control Unit, by the matron in charge of Acute Pain Management, and by ward staff.

The PCA form contains the age and gender of the patient, the type of surgery, date of onset and discontinuation of PCA, the pre-programmed PCA pump settings, the usage information, effectiveness of analgesia, side-effects experienced, and the amount of morphine discarded upon discontinuation after 24 hours. The usage information included how many times the patient pressed the on-demand button, how much intravenous morphine was delivered to the patient, and whether it was believed that the PCA device was used with insight. The effectiveness of analgesia was measured through a 10-point numeric pain scale and breakthrough pain medication given. The presence of nausea, pruritis, urine retention and headache were documented as side-effects on the form. Correct and complete documentation of the forms were also observed.

This form is stored in the patients file for record keeping. Ethical approval was obtained from the Health Sciences Research Ethics Committee of the University of the Free State (UFS-HSD2018/1160/2711) and the Free State Department of Health (FS_201810_008). These records were requested from the Record Department and the PCA forms were reviewed by the researcher. The information obtained from the records were captured anonymously into an electronic Excel data worksheet (see Appendix F). Statistical analysis of the data was done by the Department of Biostatistics of the University of the Free State.

RESULTS

A total of 155 patients who received intravenous morphine patient-controlled analgesia during the period 2015 to 2017 were included in the study.

The data for the continuous variables is presented in Table 1 below.

Table 1: Continuous variables

Variable	n	Median	Lower Quartile	Upper Quartile	Minimum	Maximum
Age	147	55.0	38.0	64.0	20.0	82.0
Morphine Total Dosage (mg)	154	22.75	10.0	41.0	0	122
Total Demands	152	39.0	15.0	96.5	0	2126.0
Total Good Demands	150	21.0	10.0	40.0	0	126.0
Morphine Solution Discarded (ml)	151	60.0	40.0	80.0	0	90.0

The median age of patients who received intravenous morphine patient-controlled analgesia, was 55 years with an interquartile range (IQR) of 38 – 64 years. The youngest patient was 20 years old and the oldest patient 82 years.

The total median dosage of morphine used per patient over a 24-hour period was 22.75 mg with an interquartile range of 10.0 – 41.0 mg. The minimum dosage was 0 mg and the maximum dosage was 122 mg morphine received.

The median total demands per patient was 39.0 with an interquartile range of 15.0 – 96.5 demands over 24 hours. The minimum total demands were 0 with a maximum of 2 126 demands.

The median total good demands per patient were 21.0 with an interquartile range of 10.0 – 40.0 demands over 24 hours. The minimum total good demands were 0 with a maximum of 126 total good demands delivered.

The median morphine solution discarded per patient was 60.0 ml with an interquartile range of 40.0 – 80.0 ml morphine over a 24-hour period. The minimum volume of morphine discarded was 0 ml and the maximum 90.0 ml.

The data for the categorical variables related to sex is presented in Table 2 below.

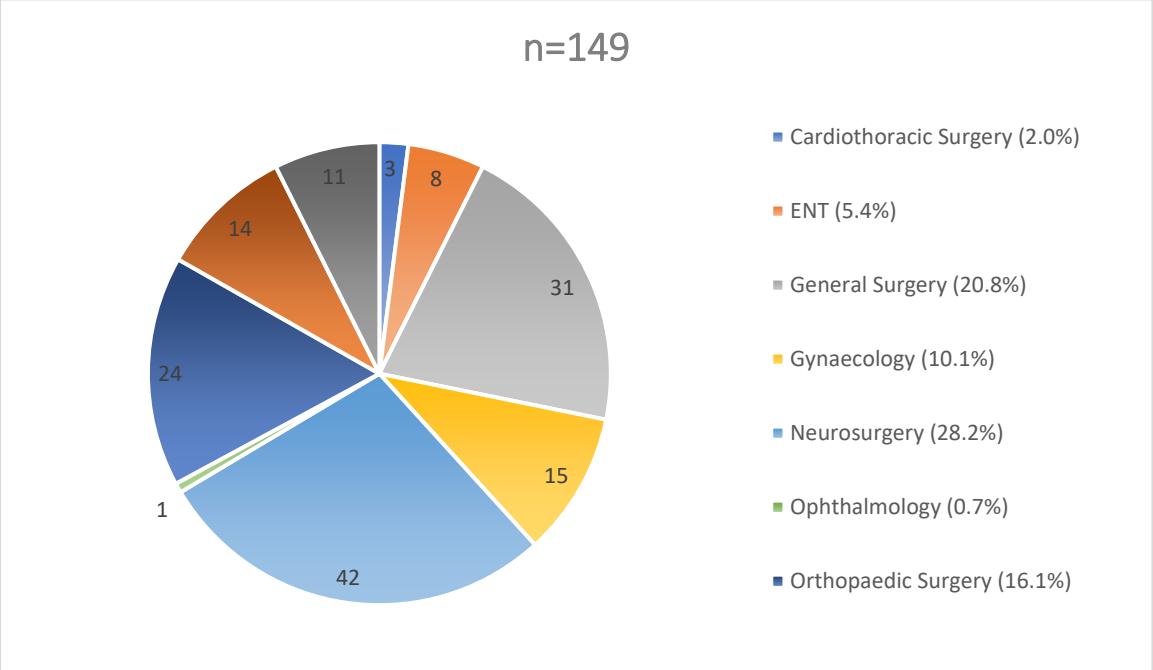
Table 2: Sex

Variable	Category	Frequency	Percent
Sex	Female	70	48.6%
	Male	74	51.4%
	Missing	11	

The sex of only 144 patients who received intravenous morphine PCA were recorded on the PCA forms with seventy (48.6%) being females and seventy-four (51.4%) males, respectively. In eleven patients, the sex was not recorded.

The categorical variables related to surgical discipline who received intravenous morphine PCA are summarized in Chart 1 below.

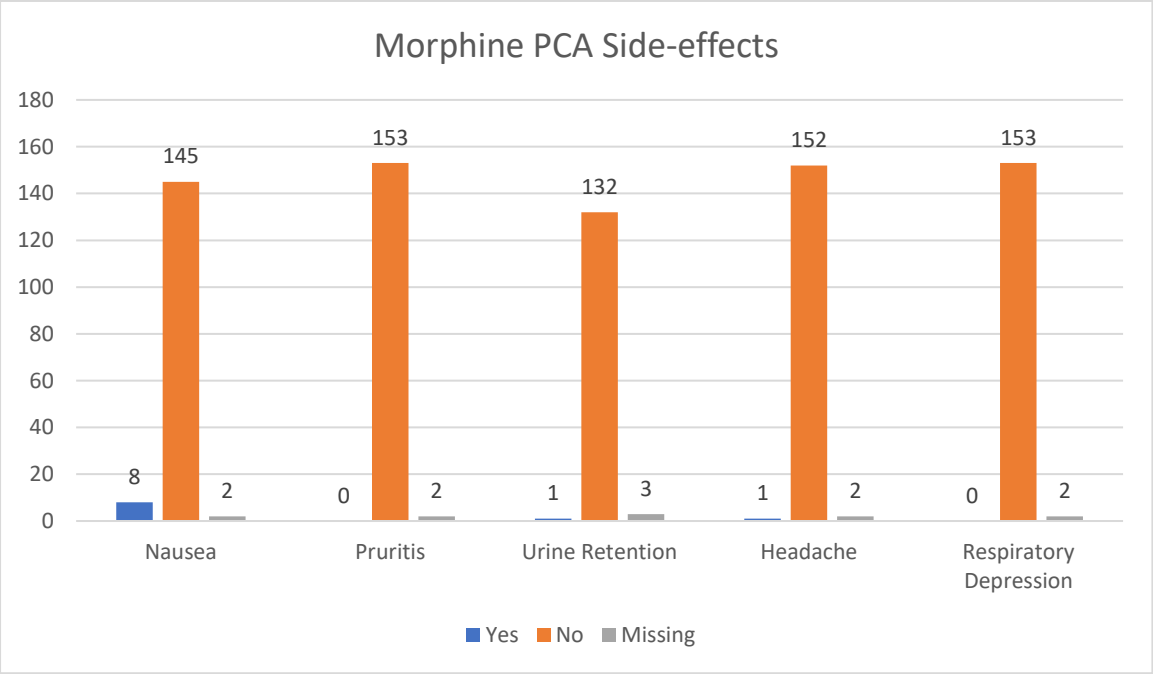
Chart 1: Surgical disciplines



Intravenous morphine patient-controlled analgesia was largely used for neurosurgical procedures (28.2%) which mostly comprised of lumbar spine laminectomies and fusions. General surgical patients accounted for 20.8% of the study population who received morphine PCA, followed by orthopaedic surgical patients with 16.1% respectively. In 6 patients who received morphine PCA, the surgical procedure performed were not documented on the PCA form.

The side-effects experienced with intravenous morphine patient-controlled analgesia are displayed in Chart 2 below.

Chart 2: Side-effects of intravenous morphine PCA



Of the 155 patients who received morphine PCA, only 19 patients (12.5%) were charted to have had urinary catheters in situ. In 3 patients, urinary output and urine retention was not recorded.

The results for insufficient analgesia, breakthrough pain medication administered, and PCA used with insight, are displayed in Table 3 below.

Table 3: Insufficient analgesia, breakthrough pain medication administered, and PCA used with insight

Variable	Category	Frequency	Percent
Insufficient Analgesia	Yes	20	13.1%
	No	133	86.9%
	Missing	2	
Breakthrough Pain Medication Administered	Yes	34	22.2%
	No	119	77.8%
	Missing	2	
PCA used with Insight	Yes	117	76.5%
	No	36	23.5%
	Missing	2	

Thirty-four patients (22.2%) who received intravenous morphine patient-controlled analgesia also received breakthrough pain medication, while only twenty patients (13.1%) reported insufficient analgesia from PCA usage. 86.9% of patients (n=133) reported sufficient analgesia with morphine PCA usage and 77.8% of patients (n=119) not requiring the administration of breakthrough pain medication.

The intravenous morphine PCA device was used with insight by 117 patients (76.5%). Only 36 patients (23.5%) were recorded to use the PCA device with poor insight.

Only 83 (53.6%) of the PCA record forms were being assessed as correct and completely documented. Seventy-two of the PCA forms (46.5%) were incomplete and inadequately documented.

DISCUSSION

The development of intravenous morphine patient-controlled analgesia has led to more effective management of acute postoperative pain, especially in older patients with more comorbid conditions, where a more controlled administration of opioid analgesia is preferred.[8] This was evidenced in our study where the average age of patients getting intravenous morphine PCA was 55 years and above. There were no gender differences observed and morphine PCA was used evenly among men (51.4%) and woman (48.6%).

Other modalities of pain management like neuraxial and regional techniques also provide efficacious control of post-surgical pain versus morphine PCA.[20] These techniques are

sometimes difficult to perform and contraindicated in patients taking anticoagulation therapy or patients with preexisting neurological deficits. Intravenous morphine patient-controlled analgesia remains the gold standard for treating pain in these patients, as our study showed that the highest use of morphine PCA was among patients getting neurosurgical procedures including spinal decompression and fusion surgery, general surgery including vascular surgery, and orthopaedic surgery, especially patients getting arthroplasty surgery.

Intravenous morphine PCA use has proven to be very safe with the device having multiple built-in safety mechanisms and alarms to prevent patient morbidity and adverse outcomes.[9] This is supported by our study, as no adverse events due to morphine PCA were documented.

Previous studies have found that intravenous morphine patient-controlled analgesia is preferred over traditional or conventional nurse administered intramuscular or intravenous opioid analgesia with better control of pain and greater patient satisfaction.[19] This is supported by our study which showed that 86.9% (133 patients) reported having sufficient analgesia and 77.8% (119 patients) not requiring the administration of breakthrough pain medication. Those patients who reported insufficient analgesia and received breakthrough pain medication, had consistent pain scores below 5 out of 10 using the visual analog pain scale. The PCA devices were also adjusted accordingly to reduce their level of pain.

The occurrence of opioid based side-effects from PCA use are exceedingly rare and can further be decreased by correctly adjusting the programmable parameters available on the device.[8] The patients in our study experienced minimal to no side-effects from intravenous morphine patient-controlled analgesia. Only 5.2% of patients in the study experienced nausea and was treated symptomatically with anti-emetics which forms part of the standard treatment protocol with intravenous morphine patient-controlled analgesia. Respiratory depression was not reported in any of the patients.

For patients to receive maximal benefit from intravenous patient-controlled analgesia, it is necessary to have a dedicated Pain Control Unit and to provide regular training to medical staff who take care of patients with morphine PCA devices.[8] Patients also need training, so they understand and know how to use the device properly. We found that 76.5% of patients (n=117) used the morphine PCA device with correct insight. 23.5% of patients (n=36) had no or minimal insight into using the device. This was also evidenced by the total demands where one patient had pressed the on-demand button a total of 2 126 times during a 24-hour period. This can be ascribed to the patient experiencing severe debilitating pain or not understanding use of

the PCA device. This was contrasted by other patients who did not use the morphine PCA device once, with 0 total demands documented.

At Universitas Academic Hospital in Bloemfontein, the intravenous morphine PCA protocol prescribes diluting morphine 90 mg to a total volume of 90 ml with sterile water for injection. This equates to a concentration of morphine 1 mg per 1 ml of the solution (morphine 1 mg/ml). The median morphine solution discarded per patient after 24-hours was 60 ml (interquartile range 40.0 – 80.0 ml) with a maximum of 90 ml morphine being wasted. The median morphine total dosage received per patient over a 24-hour period was 22.75 mg morphine (interquartile range 10.0 – 41.0 mg). This equates to the wastage of about 60 mg morphine per patient after 24 hours of using intravenous morphine patient-controlled analgesia.

LIMITATIONS OF THE STUDY

The researcher assessed the completeness and how accurately the morphine PCA forms were documented. We found that only 53.6% (n=83) of the forms were adequately completed. 46.5% (n=72) of the PCA forms were incomplete and important information was missing which can have a negative impact on patient care. Certain fields and variables were omitted or crossed out. This could potentially lead to litigation if a patient with an intravenous morphine PCA experience an adverse outcome.

IMPLICATIONS AND SUGGESTIONS

The multidisciplinary team taking care of patients with intravenous morphine patient-controlled analgesia should receive continuous and regular training to improve the quality of the PCA service rendered to patients. The team should familiarize themselves with the protocol and SOP used by Universitas Academic Hospital for the use of intravenous morphine PCA.

The protocol for intravenous morphine PCA should be revised to minimize the total wastage of morphine. The researcher suggests that a further study be done to determine the cost analysis of using intravenous morphine PCA per patient at Universitas Academic Hospital.

CONCLUSION

This study found that the average total dosage of morphine being used per patient receiving intravenous morphine patient-controlled analgesia, was 22.75 mg over a 24-hour period. The average volume morphine solution discarded per patient when the PCA device was discontinued after 24 hours was about 60 ml (equating to 60 mg morphine). Measures should be implemented to decrease this large wastage of morphine. Further research opportunities include a cost analysis study of intravenous morphine PCA usage per patient at Universitas Academic Hospital.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING

No funding source to be declared.

ETHICAL APPROVAL

Ethics approval was obtained from the Health Sciences Research Ethics Committee of the University of the Free State (UFS-HSD2018/1160/2711).

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APPENDIX A

APPROVAL FROM THE HEALTH SCIENCES RESEARCH ETHICS COMMITTEE

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

30-Oct-2018

Dear **Dr George Kotze**

Ethics Clearance: **The amount of Morphine administered per patient, for postoperative pain, using a patient-controlled analgesia (PCA) device: at Universitas Academic Hospital, Bloemfontein, from January 2015 to December 2017.**

Principal Investigator: **Dr George Kotze**

Department: **Anaesthesiology Department (Bloemfontein Campus)**

APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2018/1160/2711**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00006240; REC 230408-011; IORG0005187; FWA00012784
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa

APPENDIX B

APPROVAL FROM THE FREE STATE DEPARTMENT OF HEALTH

health
Department of Health
FREE STATE PROVINCE

22 October 2018

Dr G Kotze
Dept. of Anaesthesiology
UFS

Dear Dr G Kotze

Subject: The amount of Morphine administered per patient, for postoperative pain, using a patient-controlled analgesia (PCA) device: at Universitas Academic Hospital, Bloemfontein, from January 2015 to December 2017.

- Please ensure that you read the whole document. Permission is hereby granted for the above – mentioned research on the following conditions:
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of Universitas Hospital nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of University of Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of University of Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** lithekom@fshealth.gov.za or sebeelats@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- Please discuss your study with the institution manager/CEOs on commencement for logistical arrangements
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see http://nhrd.hst.org.za

Trust you find the above in order.
Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 23/10/18

Head : Health
PO Box 227, Bloemfotein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and, Harvey Road, Bloemfotein
Tel: (051) 408 1646 Fax: (051) 408 1556 e-mail:khusemi@fshealth.gov.za@fshealth.gov.za/chikobvup@fshealth.gov.za
www.fs.gov.za

APPENDIX C

APPROVAL FROM THE HOD OF THE DEPARTMENT OF ANAESTHESIOLOGY (UFS)

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

For attention:
Head of Department, Anaesthesiology
Dr EW Turton
16/08/2018

Request for access to patient-controlled analgesia record forms for MMed research

Dear Dr Turton,

As discussed, I would like to request access to the patient-controlled analgesia record forms for postoperative adult patients hospitalized between January 2015 and December 2017. These records will form the basis of my MMed research project.

Attached, a copy of my protocol as submitted to the HSREC for ethical approval. I will notify you when my proposal has been approved by the committee.

I am available at your convenience for any additional information required.

I trust that the request will meet with your approval and hope to make a contribution towards knowledge in the department through my research.

Regards,

Dr GPJ Kotzé
Registrar

EW Turton
HOD Anaesthesiology

KONSULTANTE/CONSULTANTS: Dr EW Turton, Proff G Lamacraft, J Diedericks, CL Odendaal, AM Kachelhoffer, Drr MA Pearson, MG Senekal, J Lemmer, NP Wessels, N van der Westhuizen, H Noeth
Department of Anaesthesiology
Departemente Anestesiologie
Lefapha la Barobatsi
T: +27 (0)51 405 3307
F: +27 (0)51 4444 3414
E: nellucia@ufs.ac.za; maribemn@ufs.ac.za
and/en Prof. BJS Diedericks) diedericksbjs@ufs.ac.za
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Parkwest/Parkwes
Bloemfontein 930
South Africa/Suid – Afrika
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Bloemfontein 9300
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UNIVERSITY OF THE FREE STATE
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YUNIBESITHI YA FREISTATA

APPENDIX D

RESEARCH PROTOCOL

1. Title

The amount of morphine administered per patient, for postoperative pain, using a patient-controlled analgesia (PCA) device, at Universitas Academic Hospital, Bloemfontein, from January 2015 to December 2017.

2. Researchers

Supervisor

Professor G Lamacraft

Head of Universitas Pain Control Unit

University of the Free State, Bloemfontein

Researcher

Dr GPJ Kotzé

Registrar

Department of Anaesthesiology

University of the Free State, Bloemfontein

3. Introduction

Intravenous patient-controlled analgesia (PCA) is one of the modalities used by anaesthesiologists to treat patients after operation for acute post-operative pain. Patient-controlled analgesia can also be used under certain circumstances to treat patients with chronic pain conditions.

By convention PCA implies administration of intravenous opioids by voluntary patient control, in an on-demand, intermittent fashion. This can be done with or without a continuous background infusion of opioids as programmed on the infusion pump. When the patient experiences pain and pushes the demand button, a pre-programmed dose of intravenous opioids is administered to the patient via a microprocessor-controlled infusion pump (Grass, 2005).

This modality of analgesia delivery provides effective pain control, fewer side effects and acceptable patient satisfaction when compared with nurse-administered parenteral opioid administration (Butterworth, et al., 2013; Chang, et al., 2004).

Other treatment modalities for postoperative pain have also proved to be as effective or even superior to intravenous patient-controlled analgesia usage. A meta-analysis found that epidural analgesia, when compared with intravenous patient-controlled analgesia, provided superior postoperative pain relief. This was found to be true for all types of surgery for which epidural anaesthesia and analgesia could be performed (Wu, et al., 2005). However, in cases where epidural anaesthesia and analgesia cannot be performed, patient-controlled analgesia is still utilised.

The use of intravenous opioid patient-controlled analgesia is not without side effects. The most common side effects of opioids being nausea and vomiting, pruritus, sedation and confusion, and respiratory depression (Sam, et al., 2011).

There are several factors that play a role in how effectively patients use a PCA device. Patient characteristics such as age, gender, weight, opioid tolerance, chronic pain and patient understanding, influence patient-controlled analgesia usage (Grass, 2005).

As regards whether intravenous patient-controlled analgesia is cost-effective compared to intramuscular (IM) analgesia - conclusive data are lacking, and further all-encompassing cost analysis studies still need to be performed regarding the cost-effectiveness of intravenous patient-controlled analgesia compared to intermittent, nurse administered IM morphine (Grass, 2005). A study done by Colwell and Morris (1995) found that in 1995, intravenous patient-controlled analgesia usage was more than twice as expensive as intramuscular injections for patients undergoing elective joint replacement. However, under staff constraints, intramuscular injections of analgesia might no be administered timeously for optimal pain management.

At Universitas Academic Hospital intravenous patient-controlled analgesia is regularly used for gynaecological, general and orthopaedic surgery and less frequently for spinal surgery. A standardized protocol regimen is used which comprises a solution of intravenous morphine 90mg diluted up to 90ml with sterile water for injection. The infusion pump is pre-programmed to deliver a bolus of 1-1.5mg morphine every time the on-demand button is pressed. Safety mechanisms, which are also programmed into the processor, include a lock out time of 8 min and a 4-hourly maximum delivery of 15-20mg morphine. The patient may also receive intermittently administered Paracetamol and Tramadol for episodes of breakthrough pain.

It has been observed at Universitas Hospital that some patients use patient controlled-analgesia more than others. Morphine must be given in a newly prepared syringe every 24 hours to minimize the infection risk to the patient. This has led to wastage of the morphine left in the syringe of the patient-controlled analgesia device when it is routinely changed or discarded after 24 hours.

The study aims to investigate the amount of morphine used over 24 hours in order to determine if the amount routinely drawn up every 24 hours should be changed to avoid wastage.

4. Aim of research

To ascertain how much intravenous morphine is being used via patient-controlled analgesia at Universitas Academic Hospital.

The objective of the study will be to determine how much morphine is required to be drawn up per 24 hours for intravenous patient-controlled analgesia, so less morphine will be wasted. This will help decide if the standard morphine patient-controlled analgesia protocol should be changed.

5. Methodology

5.1. Study design

The study will make use of an observational descriptive study design. The study will be done retrospectively.

5.2. Study participants

All patients older than 18 years that underwent surgery and received intravenous patient-controlled analgesia at Universitas Academic Hospital between January 2015 and December 2017 will be retrospectively enrolled in the study. It is estimated that approximately 180 patients will be enrolled in the study.

5.3. Measurement

It is standard practice that for every patient receiving intravenous patient-controlled analgesia, an accompanying form is completed. Sections of this form is initially filled in by the anaesthetist in theatre, and then postoperatively by the anaesthetic registrar at the Pain Control Unit, by the matron in charge of Acute Pain Management and by ward staff.

The following information is recorded on the PCA form: the age and gender of the patient, the type of operation, date of start and discontinuation of the PCA, the pre-programmed PCA pump settings, the usage information, effectiveness of analgesia and side-effects

experienced, and the amount of morphine discarded upon discontinuation. The usage information includes: how many times the on-demand button was pressed by the patient, how much intravenous morphine was delivered to the patient, and whether it was believed by the assessor that the PCA device was used with insight by the patient. The effectiveness of analgesia is measured through a 10-point numeric pain scale and the use of breakthrough pain medication. The presence of nausea, pruritis, urine retention or headache is noted as side-effects on the form. The extent to which the forms are correctly completed will also be recorded.

This form is then stored in the patients file for record keeping. These records will be obtained from medical records and then reviewed by the principal investigator. The information obtained from these records will be captured to an Excel data worksheet.

5.4. Methodological and measurement errors

Data will be collected retrospectively through overview of records. The data on the PCA forms might be incomplete, inaccurate or lost. This might lead to inadequate data collection.

5.5. Pilot study

A pilot study will be conducted using the first five cases captured to ascertain the viability of the proposed design. Upon confirmation, these cases will be included in the main study.

6. Analysis of the data

Statistical analysis of the captured data will be carried out in conjunction with the Department of Biostatistics. Results will be summarised by frequencies and percentages (categorical variables) and means, standard deviations or percentiles (numerical variables). The impact of patient variables on morphine usage and wastage will be ascertained via correlations and linear regressions.

7. Implementation of findings

From the results of this study, it shall be determined if excessive amounts of morphine for intravenous patient-controlled analgesia is being drawn up every 24 hours. The data will help decide if the PCA protocol for Universitas Academic Hospital needs changing. These results will also open possibility for further research in the field of intravenous patient-controlled analgesia at Universitas Hospital.

8. Time schedule

It is estimated that the study will be completed by the end of 2018. This protocol will be handed in for approval by the HSREC in August 2018. If the protocol is approved by the HSREC, the protocol will be submitted to the Free State Department of Health for approval. Data collection will take place for a two-week period during October 2018. Analysis of the data will be done by the Department of Biostatistics. After analysis of the data, the research report will be written and aimed for completion by end of December 2018.

9. Budget

The cost of conducting this study is estimated to be minimal, related to stationary and printing. All costs incurred will be carried by the principal investigator. No application for funding will be undertaken.

Item	Cost
Stationary	R100
Printer cartridge	R500
Ream of paper	R100
Binding	R200
Total	**R900**

10. Ethical aspects

Before the study is conducted, the protocol will be submitted for approval by the HSREC of the University of the Free State.

After approval by the HSREC, the protocol will be electronically submitted to the Free State Department of Health for permission to use patient data.

The information collected will be handled in a confidential manner and no individual or patient identifiers will be captured.

Approval by the HSREC and the Free State Department of Health will be communicated with the head of the Pain Control Unit at Universitas Academic Hospital.

11. Reporting of results

The results and findings generated from this study, will be written up in the form of a publishable article. The results will be available to Universitas Academic Hospital, Department of Anaesthesiology, the School of Medicine at the University of the Free State and the Free State Department of Health.

12. References

Butterworth, J., Mackey, D., Wasnick, J. & Morgan, G. M. M., 2013. *Morgan and Mikhail's Clinical Anesthesiology.* Fifth ed. New York: McGraw-Hill.

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Wu, C. et al., 2005. Efficacy of Postoperative Patient-controlled and Continuous Infusion Epidural Analgesia versus Intravenous Patient-controlled Analgesia with Opioids. *Anesthesiology,* 103(5), pp. 1079-1088.

APPENDIX E

INTRAVENOUS MORPHINE PATIENT-CONTROLLED ANALGESIA RECORD FORM

PATIENT CONTROLLED ANALGESIA
RECORD FORM

Patient sticker

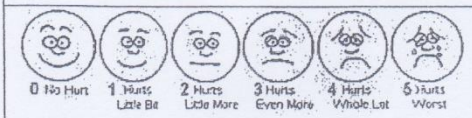
Surname
Hospital nr
Age
Ward
Adress

Operation..... Onset PCA.....

Drug Consentration	mg/ml	Drug used	
PCA Dose	mg	Lockout time	min
Continuous infusion	mg/hour	Discontinued	
4 hour Maximum dose	mg	Pain Dr	Speeddail

PATIENT FLOWCHART

Date										Action taken
Time										
Total dosage received										
Total demands										
Total good demands										
Respiration										
Sedation level 1-5 see below										
Pain level 1-10 see below										
Insufficient analgesia										
Breakthrough pain medication										
Nausea										
Pruritis										
Urine retention										
Headache										
Does the patient use the pca with insight?										
Signature										

Visual Analogue scale	Sedation level scale
	1=Comfortable 2=Sleepy 3=Intermittent Sleep 4=Asleep most of the time 5=Only awake when aroused

.....ml Morphine Solution Discarted

Signature..... Witness.....

APPENDIX F

EXCEL DATA COLLECTION FORM

Record Number	Age (years)	Sex (M/F)	Operation	Surgical Discipline	Morphine Concentration (mg/ml)	Morphine PCA Dose (mg)	4 Hourly Maximum Morphine Dose (mg)	Morphine Total Dosage Received (mg)	Total Demands	Total Good Demands	Insufficient Analgesia (Y/N)	Breakthrough Pain Medication Administered (Y/N)	Nausea (Y/N)	Pruritis (Y/N)	Urine Retention (Y/N)	Headache (Y/N)	Resp Depression	PCA Used With Insight (Y/N)	Morphine Solution Discarded (ml)	Chart Correctly Filled

APPENDIX G

INSTRUCTIONS TO AUTHORS – SOUTHERN AFRICAN JOURNAL OF ANAESTHESIA AND ANALGESIA

Login or Register to make a submission.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

- ✔ This manuscript has currently only been submitted to SAJAA and has not been published previously.
- ✔ This work is original and all third party contributions (images, ideas and results) have been duly attributed to the originator(s).
- ✔ Permission to publish licensed material (tables, figures, graphs) has been obtained and the letter of approval and proof of payment for royalties have been submitted as supplementary files.
- ✔ The submitting/corresponding author is duly authorised to herewith assign copyright to the South African Society of Anaesthesiologists (SASA).
- ✔ All co-authors have made significant contributions to the manuscript to qualify as co-authors.
- ✔ Ethics committee approval has been obtained for original studies and is clearly stated in the methodology as well as provided as a supplementary file.

- ✔ A conflict of interest statement has been included where appropriate.
- ✔ The submission adheres to the instructions to authors in terms of all technical aspects of the manuscript.
- ✔ Plagiarism: The submitting author acknowledges that the Editorial Board reserves the right to use plagiarism detection software on any submitted material.

Author Guidelines

Submitted manuscripts that are not in the correct format and without the required supporting documentation specified in these guidelines will be returned to the author(s) for correction and will delay publication.

AUTHORSHIP

Named authors must consent to publication **by signing a covering letter** which should be submitted as a supplementary file. Authorship should be based on substantial contribution to:

(i) conception, design, analysis and interpretation of data;

(ii) drafting or critical revision for important intellectual content; and

(iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to **www.icmje.org**); and

(iv) exact contribution of each author must be stated.

DECLARATION OF CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute a conflict of interest. If there is no conflict of interest to declare please include the following statement: The authors declare no conflict of interest.

FUNDING SOURCE

All sources of funding should be declared. Also define the involvement of study sponsors in the study design, collection, analysis and interpretation of data; the writing of the manuscript; the decision to submit the manuscript for publication. If the study sponsors had no such involvement, this should be stated as follows: No funding source to be declared.

RESEARCH ETHICS COMMITTEE APPROVAL

The submitting author must provide written confirmation of Research Ethics Committee approval for all studies including case reports. The ethics committee as well as the approval number should be included.

STATISTICAL ANALYSIS

Authors are advised to involve medical statisticians at the protocol stage of their research project: to plan sample size, and the selection of appropriate statistical tests for analysis and presentation.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to **www.icmje.org**.

ETHNIC CLASSIFICATION

The rationale for analysis based on racio-ethnic-cultural categorisation should be indicated.

CATEGORIES OF SUBMISSIONS

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Original articles

Original articles on research relevant to anaesthesia and analgesia should not exceed 3 200 words, no more than 30 references, with up to 6 tables or figures. A structured abstract under the following headings, Background, Methods, Results, and Conclusions is a requirement and should not exceed 300 words.

Clinical Review articles

Review articles relevant to anaesthesia and analgesia should not exceed 2 400 words, with a maximum of 20 references and no more than 6 tables or figures. A summary of 300 words or less is required.

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Case reports should not exceed 1 800 words with no more than 10 references. Figures are limited to 2 figures and may include images or photographs. The case report should have three headings: Summary (not exceeding 100 words), Case report (with no introduction) and Discussion. Case reports will be published online only. The summary and the URL will appear in the printed version.

Scientific Letters

Scientific Letters should not exceed 2 400 words with a maximum of 10 references. Only one table or illustration is permissible. A structured abstract under the following headings, Background, Methods, Results, and Conclusions, is a requirement and should not exceed 250 words.

Letters to the editor

Letters to the editor should be 800 words or less with only one image or table.

MANUSCRIPT PREPARATION

Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - **www.icmje.org**. Manuscripts must be provided in **UK English**.

Qualification, affiliation and contact details

This information must be provided for ALL authors and must be submitted as a supplementary file.

Email addresses of all author must be provided.

ORCID number of **ALL** authors must be provided – if authors do not have ORCID, please register at https://orcid.org/

Abbreviations

All abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements

Scientific measurements must be expressed in SI units except blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age) should also be preceded by a space e.g. > 20 years. No spaces should precede ± and °, i.e. '35±6' and '19°C'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160...

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting

The manuscript must be in Microsoft Word or RTF document format. Text must be 1,5-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, except for Tables). *The manuscript must be free of track changes.*

Disclaimers should follow the Conclusion and it should be in the following order:
Acknowledgements, Declaration conflict of interest, Funding source, Ethics declaration and ORCID.

ILLUSTRATIONS AND TABLES

If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

Tables may be embedded in the manuscript file **and** provided as **'supplementary files'**. They must be numbered in Arabic numerals (1,2,3...) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes, tabs or enters) and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Figure 1)'. Figure legends: Figure 1: 'Title...'. All illustrations/figures/graphs must be of **high resolution/quality**: 300

dpi or more is preferable, but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached as '**supplementary files**' upon submission (not embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft PowerPoint or Excel must be accompanied by the original workbook.

REFERENCES

Authors must verify references from the original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists may be generated with the use of reference manager software, but the final document must be delinked from the reference database or otherwise generated manually. Citations should be inserted in the text as superscript, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6] The superscript reference number should come after the punctuation mark and should not be in brackets.

All references should be listed at the end of the article in numerical order of appearance in the **Vancouver style** (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus. Names and initials of all authors should be given; if there are more than six authors, the first four names should be given followed by et al. First and last page, volume and issue numbers should be given. **Wherever possible, references must be accompanied by a digital object identifier (DOI) link and PubMed ID (PMID)/PubMed Central ID (PMCID).** Authors are encouraged to use the DOI lookup service offered by **CrossRef**. Crossref DOIs should always be displayed as a full URL link in the form https://doi.org/10.xxxx/xxxxx

Journal references:

1. Jun BC, Song SW, Park CS, Lee DH. The analysis of maxillary sinus aeration according to aging process: volume assessment by 3-dimensional reconstruction by high-resolutional CT scanning. Otolaryngol Head Neck Surg. 2005 Mar;132(3):429-34.
2. Polgreen PM, Diekema DJ, Vandeberg J, Wiblin RT, et al. Risk factors for groin wound infection after femoral artery catheterization: a case-control study. Infect Control Hosp Epidemiol [Internet]. 2006 Jan [cited 2007 Jan 5];27(1):34-7. Available from: http://www.journals.uchicago.edu/ICHE/journal/issues/v27n1/2004069/2004069.web.pdf.

Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101. *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

Other references (e.g. reports) should follow the same format: Author(s). Title. Publisher place: publisher name, year; pages. Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'. Unpublished observations and personal communications in the text must not appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

COVERING LETTER

A covering letter to the editor is mandatory and must include statements that the manuscript has not been published previously and is not under review elsewhere. It should state details of any prior publication of the research in abstract form or in Congress proceedings. The letter must declare if any of the authors have a conflict of interest and that the requirements for submission, including ethics approval and patient permission for case reports have been fulfilled. All authors must sign the covering letter.

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Manuscripts, after vetting by the editorial team, are assigned for peer-review to 2 reviewers, conversant with the particular field of research. The reviewers and the authors are blinded to each other's identity. The turn-around time for review and initial editorial decision notification aims to be within 6 weeks of submission.

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APPENDIX H

TURNITIN PLAGIARISM SUMMARY REPORT

The amount of Morphine administered per patient, for postoperative pain

ORIGINALITY REPORT

12%	10%	8%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet Source	3%
2	Submitted to University Of Tasmania Student Paper	1%
3	journals.lww.com Internet Source	1%
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9	documents.mx	

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20	Rathmell, J.P.. "Acute Post-Surgical Pain Management: A Critical Appraisal of Current Practice", Regional Anesthesia and Pain Medicine, 200607 Publication	<1%
21	"Perioperative Medicine", Wiley, 2012 Publication	<1%
22	N. Rawal. "Current practices for postoperative pain management in Europe and the potential role of the fentanyl HCl iontophoretic transdermal system", European Journal of Anaesthesiology, 04/2007 Publication	<1%

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26	www.deepdyve.com Internet Source	<1%
27	www.scribd.com Internet Source	<1%
28	Kong, Ben, and â€,Jacques T. Ya Deau. "Patient-controlled analgesia", Essentials of Pain Medicine, 2011. Publication	<1%
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