Carbon dioxide levels of ventilated adult critically ill post-operative patients on arrival to the intensive care unit

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

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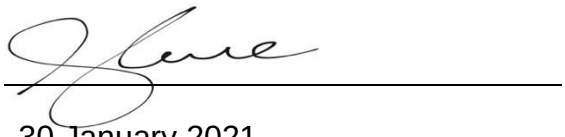
Declaration

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



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Abstract

Background

The transportation of critically ill patients presents a precarious situation in which adverse events may occur. At Chris Hani Baragwanath Academic Hospital (CHBAH) patients were manually ventilated using a manual resuscitator bag during transportation from theatre to the ICU. The aim of this study was, therefore, to evaluate the arterial carbon dioxide ($PaCO_2$) levels of ventilated adult critically ill post-operative patients on arrival to the ICU at CHBAH.

Methods

This was a cross-sectional study using convenience sampling. Pre- and post-transportation arterial blood gases were obtained from 47 patients.

Results

There was a statistically significant difference in the pre- and post-transport $PaCO_2$ level ($p= 0.03$), with a mean difference of 3.3 mmHg. The pre- and post-transport PaO_2 level ($p= 0.0002$) and the week and weekend $PaCO_2$ pre-transport ($p= 0.00$) and post-transport ($p= 0.01$) were statistically significantly different. No statistically significant difference was found in the other arterial blood gas parameters or in the post-transport $PaCO_2$ of those patients, 26 (55%), who received a neuromuscular blocking drug compared to those that did not. Adverse events were noted during 12 (26%) of the transports, 5 (41.7%) of which were patient-related, and 7 (58.3%) of which were infrastructure-related.

Conclusion

There was a statistically but not clinically significant difference in the $PaCO_2$ level pre- and post-transport and between week and weekend transportations. Hypercarbia was the most common derangement in all transports. Adverse events occurred during one quarter of transportations.

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Abbreviations

ABG	Arterial blood gas
AMBU	Artificial Manual Breathing Unit™
CHBAH	Chris Hani Baragwanath Academic Hospital
FiO_2	Fraction of inspired oxygen
HCO_3	Bicarbonate ion concentration
ICU	Intensive care unit
MRB	Manual resuscitator bag
$PaCO_2$	Arterial partial pressure of carbon dioxide
PaO_2	Arterial partial pressure of oxygen
PEEP	Positive end-expiratory pressure
SaO_2	Arterial oxygen saturation

Statement

The Research Report consists of a literature review, draft article, study proposal and appendices. The study proposal is included for background reference and is not for examination.

The formatting of this Research Report complies with the University of the Witwatersrand's Style Guide for Theses, Dissertations and Research Reports. The formatting of the draft article may differ from the author guidelines of the Southern African Journal of Critical Care, the journal to which it is intended to be submitted, in order to comply with the university's style guide.

Section 1: Review of the literature

1.1 Introduction

In this literature review the following topics will be discussed; background of the transportation of critically ill patients and adverse events occurring during transportation with specific focus on the respiratory adverse events and the influence of the mode of ventilation on the occurrence of these respiratory adverse events.

1.2 Background

The need to transport a critically ill patient out of the safety of the controlled environment of the intensive care unit (ICU) often arises in order to access diagnostic and therapeutic services unavailable at the bedside (1-4). Patients may also be transported for admission into the ICU (5). The transport may be within the hospital premises, to various departments such as radiology or the operating theatre. This is referred to as intra-hospital transport (4, 6). Transfer between hospitals for more specialised services at centralised care facilities is termed inter-hospital transfer (4, 7).

The transportation of critically ill patients in between and within hospitals is fraught with potential difficulties (8). This is due to a combination of patient-specific factors (1), equipment-related issues (9-11) and the transportation practices carried out by the escorting team (4, 6). According to Blakeman and Branson (4) and Shirley and Bion (11), intra-hospital transport occurs more frequently than inter-hospital transport. Intra-hospital transport patients tend to be sicker than those transferred from other facilities and may be considered too sick to survive the transfer to other hospitals. Therefore these patients are at an increased risk of complications (4, 12). The risk of complications arising from transportation must be outweighed by the potential benefit of enhancing the survival of the patient as a result of the planned intervention (3, 4, 8).

Voigt et al. (7) performed a retrospective review of all patients admitted to an oncological ICU between 2004 – 2005. The authors found a significant increase in

the severity of illness scores in transported patients compared to patients not requiring transportation. Patients who were transported were shown to have a significantly longer length of stay and higher mortality of 28% as compared to non-transported patients who had a mortality of 7%. Sub-group analysis showed that the patients requiring multiple transportations out of the ICU had a longer length of stay and a higher mortality which was not statistically significant, compared to those patients requiring only one transportation out of the ICU (7). In this study, the authors were unable to determine if the increase in complications was directly related to factors involved in the transportations or if it was the result of progression of the patients' underlying disease process (7).

Schwebel et al. (10), in 2013, reported that transported patients had longer ICU stays of 12 days vs. 5 days in non-transported patients. Transported patients had increased severity of illness scores, specifically the Simplified Acute Physiology and Chronic Health Evaluation II Score, of 51 compared to 46 in the patients who were not transported. Post-transportation complications were found in 37.4% of the patients. These complications included; pneumothorax, atelectasis, ventilator-associated-pneumonia, hypoglycaemia and hyperglycaemia. The authors concluded that intra-hospital transport increases the risk of complications in critically ill ventilated patients (10).

1.3 Adverse events during transportation

The Harvard Medical Practice Study (13) in 1991, defined an adverse event as "an injury that was caused by medical management (rather than the underlying disease) and that prolonged the hospitalization, produced a disability at the time of discharge, or both" (13).

Some studies (7, 14, 15) have shown that there is a potential for deterioration of critically ill patients' clinical condition associated with adverse events occurring during transportation. These adverse events increase the morbidity and mortality of transported patients compared to those not requiring transportation (4, 7, 15).

There is a disparity in the literature regarding the incidence of adverse events occurring during the transportation of critically ill patients (2, 8, 14, 16). The incidence ranges from as high as 79.8% (8), to as low as 6% (16). A 2015 review

by Droogh et al. (14), showed an incidence of adverse events during the transportation of critically ill patients of between 3% – 75%. The authors cited difficulties with definitions, poor record-keeping and inappropriate use of severity scores, as factors that influence the wide variation in the reported incidence of adverse events. They recommended the standardisation of definitions as well as using a validated severity score specific to the population of critically ill patients being transported. This review also described an association between the transportation of critically ill patients and worsening of the patient's clinical condition. A proportional relationship was found between the duration of transfer, severity of illness, inexperience of the team performing the transfer and an increase in adverse events. Cardio-respiratory incidents were found to be the most common adverse event. Cardiovascular events occurred in between 6% – 24% of patients and included hypertension, hypotension, tachycardia, bradycardia and various arrhythmias. Respiratory events occurred in up to 15% of patients and included inadequate ventilation and oxygen desaturation. Other adverse events included equipment failure, power failure, gas supply problems, malfunctioning and missing equipment and these events occurred during the transport of between 9% – 36% of patients (14).

In other studies (1, 8, 9, 11,12), factors contributing to adverse events encountered during patient transfer included; physiologic derangements (1, 8), less sophisticated monitoring and support equipment used during transport (9, 11, 12), physical movement of the patient with its risks of disconnecting lines and inadvertent extubation (12), lack of a dedicated transport team, lack of proper planning and preparation during transportation and altered environmental factors (12).

Shirley and Bion (11), highlighted the downgrading of intensive care support during transfer, and a lack of back-up equipment (9, 11, 12) as causes of adverse events during the transportation of critically ill patients. Most healthcare facilities reserved the sophisticated and up to date equipment for theatre and ICU, leaving unreliable and out-dated equipment to be used during transport, in order to mitigate the risk of loss or damage of the equipment in transit (9, 11,12). Blakeman et al. (4) specified battery failure as the most common cause of equipment failure.

Beckmann et al. (9) observed that adverse events occurred in 31% of transportations. These included major physiologic derangements in 15% of the transported patients, patient dissatisfaction in 7%, prolonged hospital stay in 4% and physical or psychological injury in 3% with death occurring in 2% of the transported patients. Some of the adverse events noted were caused by equipment problems in 39% of the transported patients, while errors made by the transporting team accounted for 61% of the adverse events. Of all the problems identified, 46% were systems related and 54% were human-based problems (9).

Two South African studies reported adverse events during transport of critically ill patients. Geldenhuys et al. (17) in Pietermaritzburg, investigated the effect of an intra-hospital transfer protocol on the safety of critically ill patients in two hospitals. The authors found an initial incidence of adverse events of 58.3%, which only decreased to 56.1% after introduction of the transfer protocol. In Durban, Seilbea and De Vasconcellos (18) investigated adverse events occurring during the intra-hospital transport of patients in one hospital. The authors reported that adverse events occurred in 23.4% of transportations, 55% of which were patient-related and 45% were technical. Hypotension, at 55%, was the most frequently reported patient-related adverse event. An increased mortality (63.6%) was observed in those patients in whom adverse events occurred compared to those in whom there were no adverse events (30.6%).

As is evident from the literature, adverse events are common during the intra-hospital transfer of patients (8, 9, 12, 14). Physiologic derangements account for a significant proportion of the adverse events (1, 8, 9). Of these physiologic derangements respiratory adverse events are the main focus of this review and will be discussed in further detail.

1.4 Respiratory adverse events

In 2016, De Vasconcellos et al. (5), described the incidence of hypoxaemia on arrival in a multi-disciplinary ICU. The study was performed as a retrospective observational review of data obtained during a prospective audit at King Edwards Hospital in Durban, South Africa. The authors found that of the 148 transports that occurred, 15.5% of patients were hypoxemic on arrival in the ICU and 17% of

these had major adverse airway events. Patient-dependent factors, such as the referring discipline that the patient was transported from, were identified as significant risk factors. The lack of skill of personnel conducting the transport, in the form of inexperienced interns, was also found to be a significant risk factor. During risk factor analysis, patients who were transported without oxygen saturation monitoring had a 37% risk of hypoxaemia compared to 13% for those who had oxygen saturation monitoring and this was statistically significant. Lack of oxygen saturation monitoring was found to be the only independent risk factor for hypoxaemia on multivariate analysis (OR 6.1 95% CI 1.5-24.5). One of the confounding factors was the possibility of underlying cardio-respiratory pathology, which could result in decreased arterial oxygen saturation independent of the adequacy of the ventilation and oxygenation during transportation (5).

Hyperventilation and respiratory alkalosis have been described as being the more common respiratory derangements following the use of a manual resuscitator bag (MRB) during the transportation of a critically ill patient (19, 20). The use of MRBs without tidal volume meters (volumeters) may predispose critically ill ventilated patients to respiratory alkalosis during transportation. This is because the individual administering the ventilation is unaware of how much tidal volume is being delivered with each compression of the MRB and because lung compliance varies within different patients (19, 21).

In 2005, Turki et al. (21), found that tidal volumes ranging between 400 ml – 1000 ml were administered by nine experienced respiratory therapists, during manual ventilation of a test lung with variable resistance and compliance. The frequency of breaths delivered averaged 25 breaths per minute in the study. The pressure generated by the respiratory therapists during manual ventilation ranged from 18 cmH_2O to over 100 cmH_2O, with the majority of the pressure readings falling above the safe limit of 40 cmH_2O (21). The authors recommended the use of MRBs with real-time measurement of the airway pressures generated or the use of mechanical transport ventilators (21).

Hurst et al. (19) compared the arterial blood gases (ABGs) of 28 patients ventilated during transportation, either using an MRB or a transport ventilator. The authors noted an increase in baseline pH from 7.39 to 7.51 and a decrease in arterial partial pressure of carbon dioxide ($PaCo_2$) from 39 mmHg to 30 mmHg, both of which were significant. Two of the patients in the MRB group developed cardiac arrhythmias. The authors recommended the use of portable transport ventilators (19).

Gervais et al. (20) randomised 30 intubated patients undergoing transportation into three groups of 10 patients each. The first group received conventional manual ventilation with an MRB. The second group received manual ventilation with an MRB modified by the addition of a volumeter at the exhalation valve. The third group received mechanical ventilation using a transport ventilator set according to the ICU ventilator settings. ABG analysis was done pre-transportation and repeated after the transportation. Both the conventional manually ventilated group and the mechanically ventilated group showed a significant decrease in $PaCO_2$ and a significant increase in pH. The group ventilated with an MRB modified by the addition of a volumeter showed no significant changes in ABG parameters. These findings led the authors to recommend the monitoring of minute ventilation during transportation (20).

There was no change noticed in arterial oxygenation parameters in the studies by Hurst et al. (19) and Gervais et al. (20). This implies that focusing solely on hypoxaemia as a marker for inadequate ventilation and oxygenation in transit may miss other ventilatory problems that do not produce hypoxemia (22).

Braman et al. (23) transported 36 intubated patients and noted a significant difference in ABG values in the 20 manually ventilated patients, compared to the 16 patients who were mechanically ventilated using a transport ventilator. Haemodynamic changes as a result of alterations in the ABG parameters were observed in the manually ventilated patients, with hypotension and arrhythmias being significantly associated with the ABG abnormalities.

1.5 The influence of mode of ventilation on respiratory adverse events

According to Blakeman and Branson (4), historically, manual ventilation using MRBs was the preferred method of ventilating intubated patients requiring artificial ventilation during transportation, due to the unreliable performance of transport ventilators prior to 2001. Ventilatory failure, big bulky devices that were impractical to manoeuvre, unacceptably high fresh gas consumption, as well as prohibitively short battery lifespans with electrical failure occurring unexpectedly, meant mechanical transport ventilators were less reliable and more cumbersome to use during transportation than MRBs (4, 24).

The United States Food and Drug Administration agency approved the use of portable transport ventilators in 2001 (24). Blakeman and Branson (4), in 2013, evaluated the performance of four commonly used mechanical transport ventilators and discovered a wide variation in their performance. Some of the ventilators had inaccurate tidal volumes towards the end of their battery life, while others could not deliver synchronous or assisted modes of ventilation. High fresh gas consumption was also noted (4). These factors could potentially induce hypercarbia, increase the work of breathing for spontaneously breathing patients and increase the cost associated with their use in terms of high oxygen cylinder turnover (4). Nevertheless, due to the advent of modern, sophisticated, portable transport ventilators (24), it is now easier and more efficient to use transport ventilators as opposed to MRBs for multiple reasons that will be discussed in further detail.

Most MRBs do not have an oxygen blender attachment to control the fraction of inspired oxygen (FiO_2) delivered to the device. The fresh gas flow through the MRB is obtained directly from the oxygen cylinder or wall pipeline (24). MRBs are specifically designed to deliver an FiO_2 of close to 100% due to the strategic positioning of valves and high fresh gas flow which reduce the entrainment of room air (24, 25). The inability of the MRB to dilute the FiO_2 produces hyperoxia, which can result in oxygen toxicity (24). Hyperoxia produces changes in haemodynamics, alterations to coronary blood flow and oxygen free radicals which exacerbate lung injury via oxidative stress (24).

Dangerously high airway pressures can occur during the use of MRBs without an airway pressure monitoring gauge (21). Excessive airway pressure can result in barotrauma, dynamic hyperinflation and pneumothorax (21, 26). Variable respiratory rate and tidal volume are common during the use of an MRB, resulting in inconsistent minute ventilation that can produce sub-optimal ventilation and volutrauma (4). Sub-optimal ventilation causes respiratory derangements that alter the patient's acid-base status and can be arrhythmogenic and may adversely affect the patient's haemodynamic stability (19).

The inability to maintain positive end-expiratory pressure (PEEP) resulting in lung de-recruitment and atelectasis when using MRBs without a PEEP valve is a problem that can lead to hypoxaemia (4, 21). Some types of MRBs have been shown to cause substantial increases in airway resistance and thereby increase the work of breathing for spontaneously breathing patients (4, 24, 27).

During the transportation of intubated and ventilated critically ill patients, if muscle relaxants are not used, the combination of the highly stimulating period of patient movement accompanied by a relative period of infrequent drug dosing in terms of sedatives and analgesics, may trigger the patient to attempt spontaneous breathing. Dyssynchrony could develop between the patient's attempts at breathing and the timing of the breaths delivered by the healthcare worker administering the ventilation (4, 5, 24). De Vasconcellos et al. (5) noticed significant improvements in respiratory parameters in patients who were paralysed with muscle relaxants prior to transportation and manual ventilation (5). If the patient is allowed to breathe spontaneously on an MRB, the increased resistance and subsequent increased work of breathing could increase the patient's myocardial oxygen demand, add stress to the patient and cause discomfort, tachycardia, tachypnoea or exhaustion (4, 24, 27).

Mechanically ventilated critically ill patients are at risk of acute lung injury or acute respiratory distress syndrome (19, 24) and ventilator-associated-pneumonia (28). This risk may be exacerbated by the use of an MRB (24, 28). Despite these factors and the wide availability of transport ventilators for adult and paediatric use, MRBs remain the most commonly used method of ventilating patients between theatre and ICU due to their ease of use and accessibility (4, 26, 29).

Nakamura et al. (30) compared patients escorted by ICU physicians performing manual ventilation to transport ventilators in 16 patients being transported from the ICU. They found that patients being manually ventilated had significantly higher respiratory rates than those being mechanically ventilated during transportation (32 breaths versus 19 breaths, respectively). The mean tidal volumes and PEEP levels in the manually ventilated group varied significantly compared to the mechanically ventilated group. The authors concluded that the use of a transport ventilator produced more consistent ventilation with less chance of deterioration of the patient's respiratory parameters (30). However, different physicians ventilated each of the manually ventilated patients and this could be a confounding factor. These authors suggest that despite having experience, skills and expertise in manual ventilation, ICU physicians are inferior at providing optimal and predictable minute ventilation with the use of an MRB in comparison with a mechanical transport ventilator (24, 30).

While most studies (4, 17, 18, 24, 26, 27, 31) have shown that manual ventilation is neither safe nor effective and is associated with an increase in adverse events particularly with the use of MRBs, other studies have failed (24, 29, 32) to demonstrate a significant change in outcome. Rajasekaram et al. (29) measured the ABG values and haemodynamic parameters of 99 patients on arrival in a cardiac ICU to determine whether hypoventilation during transportation adversely affected physiologic indices. Of their patient population, 11.1% were transported using a transport ventilator and the rest were manually ventilated using an MRB. The authors described an overall incidence of hypocarbia (defined as a $PaCO_2$ < 35 mmHg) of 18.2%, and hypercarbia (defined as a $PaCO_2$ > 45mmHg) of 28.3%. The hypercarbia was positively and significantly correlated with an arterial acidosis (defined as a pH < 7.35). In a univariate regression model, transportation using an MRB was found to be a positive predictive factor for hypercarbia. Routine use of a transport ventilator was found to be significantly less likely to result in hypercarbia, furthermore, these patients were significantly less likely to suffer a complication during their ICU stay. Although pulmonary hypertension was common in the patient population, there was no association between $PaCO_2$ and pulmonary arterial pressure. Contrary to expectation, neither hypercarbia nor high mean

pulmonary artery pressures were associated with an increase in adverse outcomes (29).

In a similar study by O'Brien et al. (32), 36 patients were investigated for haemodynamic compromise following arrival in a cardiac ICU after being randomised into mechanical ventilation using a transport ventilator and manual ventilation using an MRB. There was a significant difference in end-tidal carbon dioxide in the group who were manually ventilated compared to those who were mechanically ventilated of 2.74 mmHg but this did not translate to a difference in the haemodynamic parameters between the two groups (32).

These studies (4, 24, 29, 32) suggest that although there might be a benefit to mechanical ventilation as opposed to manual ventilation in terms of maintaining a normal range of ventilatory indices, this may not always correlate with a statistically or clinically significant increase in adverse events. This finding is of importance in resource-limited healthcare systems because the cost of a transport ventilator is considerably greater than that of an MRB in the short term (31). However, the majority of the data do report potential harm as a result of the use of MRBs, therefore the economic implications of potentially increased adverse events with the use of MRBs must be weighed against the cost of procuring mechanical transport ventilators. Ultimately, improving outcomes through avoidance of the possible adverse effects of manual ventilation may offset the costs of mechanical transport ventilators (24).

1.6 Ventilation monitoring

Monitoring of the quality of ventilation during transportation depends on the accurate measurement of $PaCO_2$ or it's surrogate during the transportation, as $PaCO_2$ is inversely proportional to alveolar ventilation according the Alveolar Gas Equation (33). Different measurement tools are available commercially with varying levels of accessibility. The measurement tools differ in their level of invasiveness and accuracy (22, 34, 35, 36). Various studies have attempted to interrogate which measurement tool may be most appropriate for critically ill patients undergoing transportation (1, 34, 35, 36).

Palmon et al. (34), demonstrated no significant difference in overall $PaCO_2$ in pre-transport and post-transport ABG samples from patients who were manually ventilated and had continuous end-tidal capnography, compared to those that did not have continuous end-tidal capnography, and those in whom the healthcare professional administering ventilation was blinded to the capnograph value. The authors did notice a significant change in the $PaCO_2$ levels in individual patients who were not monitored for end-tidal capnography. The authors concluded that end-tidal capnography was beneficial in the transportation of critically ill patients who required tight $PaCO_2$ level control, such as traumatic brain injury patients, but showed no significant difference in patients who did not require tight control and therefore, concluded that continuous capnography is not required in short transportations (34). Two other publications supported these findings (1, 36).

Hinkelbein et al. (35), determined that $PaCO_2$ measurements during inter-hospital transportation using portable ABG analysis machines was equivalent to transcutaneous carbon dioxide measurements and superior to end-tidal carbon dioxide capnometry in terms of accuracy when compared to a reference $PaCO_2$ obtained from a conventional blood gas machine prior to transfer. This could be as a result of the problems inherent in gas module sampling; such as water inside the sample line, kinked sample lines, rebreathing as well as the frequent calibrations required to maintain the module's accuracy (22). ABG analysis is not without its difficulties, problems such as incorrect calibration and exposure of the sample to air with the subsequent diffusion of gasses out of the blood may decrease the accuracy of the result. Additionally, the variety of error margins between different machines can produce inconsistent results (37).

1.7 Summary

Transportation of the critically ill patient outside of the ICU should be seen as a continuation of intensive care and not a hiatus in it (4, 14, 38). In as far as is practically possible, the same care and attention to detail should be ongoing during transportation. Thus to continue with outdated or unsafe practices, when there is evidence in support of techniques that are superior and available would be a disservice to vulnerable critically ill patients. However, the economic implication of interventions must be weighed against the anticipated benefit of these

interventions, especially in resource-limited healthcare systems (24). The era of the “mad-dash” should be left in the military fields where transport medicine began, and there should be a move towards controlled, efficient and well-executed transports that minimise adverse events while contributing to improved patient outcomes (4, 14).

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Section 2: Author's guidelines

Southern African Journal of Critical Care

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Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

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- Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The title of the manuscript should concisely describe the study but should not include the outcome. The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. At the end of the introduction clearly state the aim or

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- In the Methods section describe in sufficient detail so that others would be able to replicate the study should they need to. Sections of the methods that have been described in previous publications need only be referenced. The statistical methods should be described. Where appropriate, sample size calculations should be included to demonstrate that the study is not underpowered.

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- The discussion should be confined to an interpretation of your results with respect to your stated aim and if applicable, a comparison to the results of similar studies. The strengths and weaknesses of your study should be discussed.

- The conclusion should be confined to an interpretation of the results of the study and a recommendation if applicable.

- May include up to 6 illustrations or tables.

- References should only include the most recent and relevant articles. A maximum of 30 references is advised.

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- This should be no more than 250 words, with the following headings:

    - **Background:** why the study is being done and how it relates to other published work.

    - **Objectives:** what the study intends to find out

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- Do not include any references in the abstracts.

- Here is an example of a good abstract.

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- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
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Acts:

- South Africa. National Health Act No. 61 of 2003.
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- South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

Bills:

- South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.
- Green/white papers:
- South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

Case law:

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From submission to acceptance

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Section 3: Draft article

Carbon dioxide levels of ventilated adult critically ill post-operative patients on arrival to the intensive care unit

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Keywords: manual resuscitation bag ventilation, transportation of critically ill patients, carbon dioxide levels

Abstract

Background

The transportation of critically ill patients presents a precarious situation in which adverse events may occur. At Chris Hani Baragwanath Academic Hospital (CHBAH) patients were manually ventilated using a manual resuscitator bag during transportation from theatre to the ICU. The aim of this study was, therefore, to evaluate the arterial carbon dioxide ($PaCO_2$) levels of ventilated adult critically ill post-operative patients on arrival to the ICU at CHBAH.

Methods

This was a cross-sectional study using convenience sampling. Pre- and post-transportation arterial blood gases were obtained from 47 patients.

Results

There was a statistically significant difference in the pre- and post-transport $PaCO_2$ level ($p= 0.03$), with a mean difference of 3.3 mmHg. The pre- and post-transport PaO_2 level ($p= 0.0002$) and the week and weekend $PaCO_2$ pre-transport ($p= 0.00$) and post-transport ($p= 0.01$) were statistically significantly different. No statistically significant difference was found in the other arterial blood gas parameters or in the post-transport $PaCO_2$ of those patients, 26 (55%), who received a neuromuscular blocking drug compared to those that did not. Adverse events were noted during 12 (26%) of the transports, 5 (41.7%) of which were patient-related, and 7 (58.3%) of which were infrastructure-related.

Conclusion

There was a statistically but not clinically significant difference in the $PaCO_2$ level pre- and post-transport and between week and weekend transportations. Hypercarbia was the most common derangement in all transports. Adverse events occurred during one quarter of transportations.

Introduction

The transportation of critically ill patients involves moving the patient from various destinations such as the emergency room, another hospital or theatre to the stable environment of the intensive care unit (ICU) (1). Transportation from the ICU to a destination outside of the ICU is often required for diagnostic and interventional procedures, which cannot be provided at the bedside (2-5). The transportation of critically ill patients presents a precarious situation in which adverse events (6) may occur (5,7). Adverse events include deterioration in the patient's haemodynamic parameters, airway and ventilator difficulties and equipment failure (5, 7-10). These adverse events may lead to an increase in morbidity and mortality in patients, arising as a consequence of the transportation challenges and not the underlying disease process (11, 12). International studies have demonstrated that portable mechanical ventilation is superior to manual ventilation using a manual resuscitator bag (MRB), during the transport of critically ill intubated patients in decreasing the risk of adverse respiratory events (2, 13-15).

MRBs do not usually have a built-in device for measuring tidal volume. The risk of hyperinflation, hyperventilation and barotrauma with the use of MRBs has been recognised (13, 15, 16). In 2005, Turki et al. (16) found peak inspiratory pressures of up to 100 cmH_2O with the use of MRBs, which are well above the suggested safe limit of 30 mmHg (40 cmH_2O) (17). Some MRBs may be modified by the addition of a tidal volume meter at the exhalation valve to estimate minute volume and control ventilation (13). Studies have indicated that the use of MRBs might result in sub-optimal ventilation of patients (5, 13, 14). The sub-optimal ventilation includes hypoventilation with a resultant hypercarbia and respiratory acidosis or the inverse, hyperventilation with hypocarbia and respiratory alkalosis. Hyperventilation with a corresponding respiratory alkalosis has been described as being the most common derangement found in patients being manually ventilated (13-15). These insults to homeostasis are deleterious to critically ill patients who may not be able to compensate adequately for these mal-adaptations (2). It is, therefore, imperative that the ventilatory transportation practices of a facility be audited frequently.

At Chris Hani Baragwanath Academic Hospital (CHBAH), the multi-disciplinary ICU is located approximately 220 m from the theatre, on two separate floors, with an elevator required for access to transport the patient to either the first floor ICU (medical and surgical patients) or the second floor ICU (trauma patients). The trajectory from the theatre to the ICU emanates from outside the theatre complex into an open-air corridor exposed to the elements. This corridor is also used as a thoroughfare for other patients, visitors, staff and supplies. This pavement surface is often damaged with potholes, due to lack of maintenance, making it difficult to manoeuvre a stretcher. There are two elevators, frequently, only one of the two is functional. This elevator is used by everyone needing to access the ICU. This causes delays as the elevator stops at every floor to load and unload passengers, during which time critically ill patients are waiting and being manually ventilated for a protracted period of time on the ground floor. When both elevators are out of service, an external cargo hoist is used to access the back entrance of the ICU. This adds a further 110 m to the journey and additionally exposes patients to the elements. Transportation may take anywhere from 5 – 25 minutes. Due to limited resources, there are no portable mechanical ventilators to transport patients from the theatre back to the ICU. The only method of ventilating patients during transport is manual ventilation with MRBs without tidal volume meters. It was not known how well patients were being ventilated, with specific reference to their arterial carbon dioxide levels ($PaCO_2$) while being transported between the theatre and ICU. The aim of this study was, therefore, to evaluate the $PaCO_2$ levels of ventilated adult critically ill post-operative patients on arrival to the ICU at CHBAH.

Methods

Approval to conduct the study was obtained from the Human Research Ethics Committee (Medical)(M180779) of the University of the Witwatersrand and other relevant authorities. A cross-sectional, prospective research design was followed.

The study population consisted of adult intubated patients, who were manually ventilated with an MRB arriving in ICU from the theatre during the study period of between 7 April – 21 September 2019. A convenience sampling method was used. The sample size was determined in consultation with a biostatistician using EpiInfo version 7.2.0.1 and was based on a South African study by De Vasconcellos et al.

(1), where the frequency of hypoxaemia, possibly indicating inadequate ventilation, of patients on arrival in ICU was 15.5%. Assuming a total population of 60 critically ill intubated and ventilated patients were being transported from theatre to ICU per month with a 5% margin of error, at a 95% confidence level, a sample size of 46 patients was estimated to have a minimum power of 80%. The inclusion criteria for this study were patients who had either an endotracheal tube or a tracheostomy tube in situ, an arterial line in place and those for whom consent had been obtained. Patients with severe acute respiratory distress syndrome (18) were excluded from the study.

As patients were incapacitated at the time of data collection, consent was obtained from the patients' family members. Deferred consent was obtained from patients when they were able to give consent and only these patients were included in the study.

A draft data collection sheet was compiled and reviewed for face and content validity by three senior anaesthesiologists, one of whom was an intensivist. The suggestions made were incorporated into the final data collection sheet. The following information was collected: date and time of transport; patient, transport and MRB characteristics; pre- and post-transport arterial blood gas (ABG); drugs administered for transport; transport ventilation variables and adverse events that occurred during transport.

One author (MS) identified patients who were scheduled to be transported to the ICU post-operatively, from the booking information available in the theatre and ICU. The pre-transport ABG sample was collected by the patient's anaesthetist, from the patient's arterial line before the patient was disconnected from the ventilator in theatre. The post-transport ABG sample was collected by one author (MS) immediately on arrival in the ICU before the patient was attached to the ICU ventilator. ABG samples were collected in a standardised manner. The pre- and-post-transport ABG samples were analysed using a single automated blood gas analysis machine (Radiometer ABL800 Basic™) within 10 minutes of collection (19) as per standard practice.

Partial ventilation occurred when the patient was spontaneously breathing and their ventilation was being supported by assisted manual breaths, while full ventilation occurred when the patient was apnoeic and received full ventilatory support using an MRB. $PaCO_2$ is inversely proportional to alveolar ventilation (20) and was used as a marker of the adequacy of ventilation. A $PaCO_2$ level between 35 – 45 mmHg was considered normal (19). Normal pH was considered to be between 7,35 – 7,45. Day hours fell between 08:00 and 16:00 and weekdays were from Monday 08:00 – Friday 16:00.

Data were analysed in consultation with a biostatistician using STATA version 15 (StataCorp, USA). Categorical variables were described using numbers and percentages and continuous variables using means and standard deviations. Continuous variables were compared using either independent or paired t-tests. A p-value of < 0.05 was considered statistically significant.

Results

Data were collected from 60 patients, of whom 13 were excluded from the study. Of these, 11 died before informed consent could be obtained from their family members, and 2 patients were transferred to other facilities before consent could be obtained. This resulted in a sample size of 47 patients. The characteristics of the patients are shown in Table 1 and the type of transport ventilation, time and duration of transport and pre-transport drugs used are shown in Table 2. Drugs to facilitate transportation were administered to 34 (72%) patients, 20 (58%) of which received a combination of drugs.

Table 1: Characteristics of patients

Characteristic	**Mean (SD)**	**Min – Max**
Age (years)	38 (15.9)	18 – 85
Sex	**Number**	**Percentage**
Male	31	66
Female	16	34
Procedure necessitating transfer		
Laparotomy	12	25
Relook laparotomy	12	25
Tracheostomy	4	8
Craniotomy	4	8
Debridement	4	8
Burr holes	3	6
Thoracotomy	2	4
Gastroscopy	2	4
Other	4	8

Table 2: Type of transport ventilation, time and duration of transport and pre-transport drugs used

	n (%)	Mean (SD)
Type of ventilation		
• Partial	4 (8)	
• Full	43 (91)	
MRB		
• PEEP valve present	8 (17)	–
○ Set PEEP level (cmH_20)	–	6.6 (3.3)
• No PEEP valve	39 (82)	–
Time of transport		
• Weekday	14 (30)	
• Weeknight	22 (46)	
• Weekend day	3 (6)	
• Weekend night	8 (17)	
Duration of transport (minutes)		
• Weekday		13.3 (3.5)
• Weeknight		11.6 (3.2)
• Weekend day		18.6 (5.6)
• Weekend night		10.2 (2.8)
Drugs used for transportation		**Dose**
• Fentanyl (mcg)	15 (32)	77 (44.6)
• Rocuronium (mg)	20 (42)	36.8 (16.6)
• Cisatracurium (mg)	6 (13)	3.5 (1.76)
• Ketamine (mg)	2 (4)	12 (10.6)
• Midazolam (mg)	21(45)	1.1 (0.3)

A neuromuscular blocking agent was administered to 26 (55%) patients prior to transportation. No statistically significant difference was found in the post-transport $PaCO_2$ of those patients who received a neuromuscular blocking drug (mean $PaCO_2$ 45.95) compared to those that did not (mean $PaCO_2$ 44.5) ($p = 0.6$).

The occurrence of normocarbia, hypercarbia and hypocarbia pre- and post-transport is shown in Figure 1.

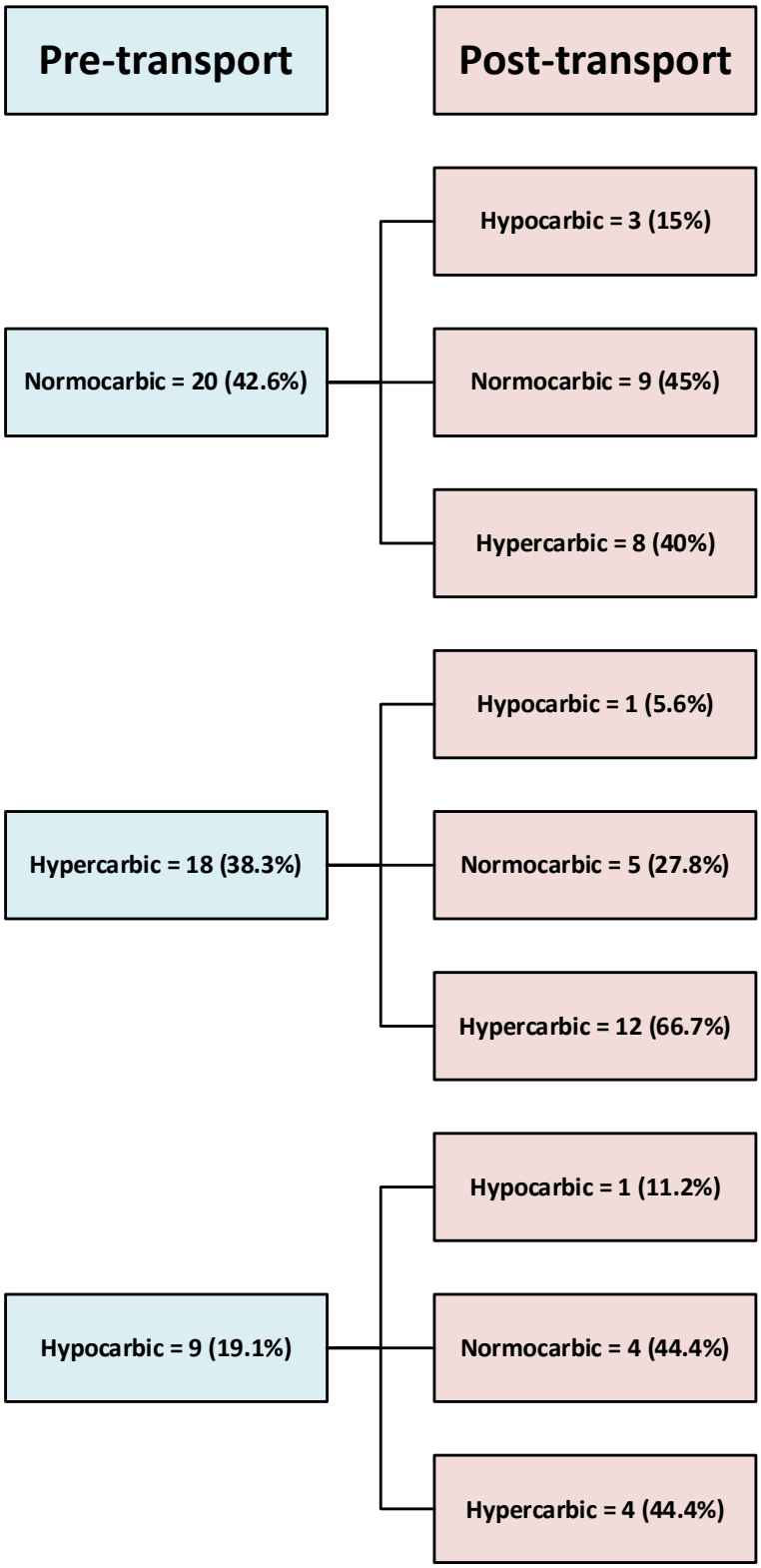

Figure 1: Occurrence of normocarbia, hypercarbia, and hypocarbia pre- and post- transport

Comparisons of the changes in the ABG values pre- and post-transportation are shown in Table 3. The fraction of inspired oxygen concentration (FiO_2) was 1.0 during post-transportation for all patients due to the lack of an oxygen/air blender device. There was a statistically significant difference in the $PaCO_2$ and the arterial partial pressure of oxygen (PaO_2) pre- and post-transport.

Table 3: Comparison between ABG parameters pre- and post- transportation

Parameter	Time	Mean (SD)	Min – Max	p-value
$PaCO_2$ (mmHg)	Pre-transport	42.0 (7.3)	27.4 – 58.9	0.03
	Post-transport	45.3 (8.9)	25.5 – 64.9	
pH	Pre-transport	7.3 (0.2)	6.6 – 7.5	0.4
	Post-transport	7.3 (0.1)	6.8 – 7.5	
HCO_3 (mmol/L)	Pre-transport	21.2 (6.8)	4.7 – 38.1	0.3
	Post-transport	21.5 (6.2)	6.3 – 35.5	
Base excess/ deficit (mmol/L)	Pre-transport	-4.7 (8.5)	-28.4 – +12.9	0.9
	Post-transport	-4.6 (7.9)	-24.8 – +9.7	
Lactate (mmol/L)	Pre-transport	4.4 (4.5)	0.7 – 18.0	0.1
	Post-transport	4.6 (4.8)	0.7 – 20.0	
PaO_2 (mmHg)	Pre-transport	124.5 (45.6)	59.9 – 263.0	0.0002
	Post-transport	175.3 (91.1)	53.3 – 430.0	
SaO_2 (%)	Pre-transport	96.8 (2.5)	88 – 100	0.5
	Post-transport	97.14 (3.5)	84.6 – 100.2	

Table 4 shows the comparisons in the $PaCO_2$ pre- and post-transport during day and night and week and weekend transportations.

Table 4: Comparison between pre- and post-transport $PaCO_2$ at different times

Time		Mean (SD)	Min – Max	p-value
				Day vs. Night
Day	Pre-transport	41.4 (8.9)	27.4 – 58.9	0.6
Night	Pre-transport	42.3 (6.3)	31.9 – 54.4	
Day	Post-transport	44.8 (6.7)	35.9 – 61.1	0.6
Night	Post-transport	45.6 (10)	25.5 – 64.9	
				Week vs. weekend
Week	Pre-transport	40.6 (7.1)	27.4 – 54.4	0.00
Weekend	Pre-transport	46.8 (6.4)	35.3 – 58.9	
Week	Post-transport	44.3 (8.7)	25.5 – 64	0.01
Weekend	Post-transport	48.7 (8.8)	38.1 – 64.9	

Adverse events were noted during 12 (26%) of the transports, 5 (41.7%) of which were patient-related, consisting of patient desaturation. Infrastructure problems accounted for the remaining 7 (58.3%) adverse events. The infrastructure problems included, elevator malfunctions (5, 71.4%) potholes on the pavement surface (1, 14.3%) and equipment failure in the form of battery failure on the monitoring device (1, 14.3%).

Discussion

Manual ventilation using MRBs without volumeters was the only mode of ventilation used to transport patients from theatre to ICU in this study. Although there was a statistically significant difference in the pre- and post-transport $PaCO_2$ level, the mean difference was only 3.3 mmHg. The physiological implications of this small difference is not clinically significant. This finding shows that although there was an increase in the $PaCO_2$, it remained within an acceptable levels, suggesting that manual ventilation with an MRB at CHBAH may not be injurious as described in some studies (13, 14, 21). The results of this study are consistent with studies by Rajasekaram et al. (22) and O'Brien et al. (23), who found that there was no clinical difference in the patients who were manually ventilated compared to those who were mechanically ventilated, despite there being a statistically significant change in the $PaCO_2$ and $EtCO_2$, respectively.

Pre-transport, the majority of patients were normocarbic (42.6%) or hypercarbic (38.3%). Post-transport, the majority (51%) of the patients were hypercarbic. This differed from the marked respiratory alkalosis that Gervais et al. (13) and Hurst et al. (14) described. This difference could be explained by various factors. Firstly, the anaesthetists at CHBAH are probably aware of the dangers of hyperventilation, and therefore deliberately tried to avoid hyperventilating the patients. Secondly, the hyperventilation could have been unintentional. Often, patients at CHBAH are transported from theatre to the ICU accompanied by only the anaesthetist and a scrub nurse. During transportation, the healthcare practitioner manually ventilating the patient may be distracted by other tasks such as manoeuvring the bed, hailing the elevator or attending to malfunctioning transportation equipment, and may be unable to deliver an adequate minute ventilation to the patient, hence producing hypercarbia. Despite hypercarbia being so common, there was no clinically relevant effect in terms of acidosis or arrhythmias reported.

The difference between week and weekend $PaCO_2$ pre- and post-transport was statistically significant. During the weekend, at CHBAH, there is an increase in trauma-related surgery and only emergency surgeries are conducted. Therefore,

patients presenting for surgery during the weekend may be sicker compared to those operated on during the week.

In this study, there was no statistically significant difference in $PaCO_2$ levels in those patients administered a neuromuscular blocking drug compared to those patients who did not. This is an unexpected finding, considering neuromuscular blockade facilitates artificial ventilation and eliminates patient-ventilator dyssynchrony. Of the 92% of patients who were fully ventilated during transportation, 55% had received neuromuscular blocking agents for transportation, however, the residual effects of drugs given during the anaesthetic may have prevented the other patients from breathing spontaneously. Additionally, sedatives and opioids have altered pharmacokinetics in critically ill patients and may produce apnoea in the presence of organ dysfunction, particularly if hepatic and renal dysfunction were present.

The PaO_2 was statistically significantly different pre- and post-transport. This difference was due to the FiO_2 being titrated to the patients' requirements in theatre, to maintain an SaO_2 between 88 – 96%, whereas all patients were transported with an FiO_2 of 1.0 due to the absence of an oxygen/air blender. Although the SaO_2 pre- and post-transport was not statistically significant, 4.3% of patients were hypoxaemic (SaO_2 <88%) on arrival in the ICU. This is lower than the 9.3% observed by De Vasconcellos et al. (1) in patients on arrival in a multi-disciplinary ICU who were transported by anaesthetists. Overall De Vasconcellos et al. (1) found an incidence of hypoxaemia of 15.5% among all patients in their study, however, not all patients were transported with a pulse oximeter. At CHBAH, the use of pulse oximetry during the transportation of patients to the ICU is mandatory. De Vasconcellos et al. (1) described pulse oximetry as a negative predictive factor for hypoxaemia.

Adverse events occurred during 26% of the transportations, this is within the range of 3 – 75% reported by Droogh et al. (24). Two South African studies reported adverse events incidences of 23.4% (25) and 56.1% (26), respectively of transported critically ill patients, the former being similar to the reported incidence in this study. Five patients were reported to have desaturated during transportation. Of these, only two patients were hypoxaemic on arrival in the ICU,

as shown on the ABG. In the three patients who arrived without hypoxaemia, the possible reasons may have included saturation probe displacement with loss of contact or the patient being vasoconstricted, causing unreliable readings. Alternatively, suspected desaturation during transportation may have been recognised and managed by hyperventilation using the MRB. Regarding the two hypoxaemic patients, one was documented as having desaturated during transportation, possibly as a result of lung de-recruitment. In the other patient the battery of the transport monitor failed during transport, however no respiratory complication was reported. Due to the infrastructure problems faced during transportation of patients at CHBAH, such as the long distance from the theatre to the ICU and the poor maintenance of the corridor and elevators, more adverse events could have been expected.

Due to the contextual design of this study, the results may not be generalisable to other contexts. Convenience sampling was used and therefore the sample may not have been representative of the population. Furthermore, the diverse pathologies of the patients may have influenced the ventilatory parameters. Based on the findings of this study, the authors recommend that in the absence of transport ventilators, MRBs equipped with PEEP valves and volumeters and oxygen cylinders fitted with oxygen/air blenders should be made available to allow better control of ventilation.

Conclusion

The purpose of this study was to evaluate the $PaCO_2$ levels of critically ill patients at CHBAH during transportation from theatre to the ICU. There was a statistically but not clinically significant difference in the $PaCO_2$ level pre- and post-transport and between week and weekend transportations. Hypercarbia was the most common derangement in all transports. Adverse events occurred during one quarter of transportations. These findings indicate that manual ventilation of critically ill patients during transport between theatre and the ICU during the study period was not injurious.

Conflict of interest

The authors declare that we have no financial or personal relationships which may have inappropriately influenced us in writing this paper.

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Section 4: Proposal

Carbon dioxide levels of ventilated adult critically ill post-operative patients on arrival in the intensive care unit

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4.1 Introduction and problem statement

The transportation of critically ill patients involves moving the patient from various destinations such as the emergency room, another hospital or theatre to the stable environment of the intensive care unit (ICU) (1). Transportation from the ICU to a destination outside of the ICU is often required for diagnostic and interventional procedures, which cannot be provided at the bedside (2-5).

The transportation of critically ill patients presents a precarious situation in which adverse events may occur (5, 6). Adverse events include deterioration in the patient's haemodynamic parameters, airway and ventilator difficulties and equipment failure (5-9). These adverse events may lead to an increase in morbidity and mortality of patients, arising as a consequence of the transportation challenges and not the underlying disease process (10, 11).

International studies have demonstrated that portable mechanical ventilation is superior to manual ventilation, using a manual resuscitator bag (MRB), during the transport of critically ill intubated patients in decreasing the risk of adverse respiratory events (2, 12-14).

MRBs do not usually have a built-in way of measuring tidal volume. The risk of hyperinflation, hyperventilation and barotrauma with the use of MRBs has been recognised (12, 14, 15). In 2005, Turki et al. (16) found peak inspiratory pressures of up to 100 cm H_2O with the use of MRBs, which are well above the safe limit of 30 mmHg (17). Some MRBs may be modified by the addition of a tidal volume meter at the exhalation valve to estimate minute volume and control ventilation.

Studies have indicated that the use of MRBs might result in sub-optimal ventilation of patients (5, 12, 13). The sub-optimal ventilation includes; hypoventilation with hypercarbia and respiratory acidosis or the inverse, hyperventilation with hypocarbia and respiratory alkalosis. Hyperventilation with a corresponding respiratory alkalosis has been described in the literature as being the most common derangement found in patients being manually ventilated (12-14). These insults to homeostasis are deleterious in critically ill patients who may not be able

to compensate adequately for these mal-adaptations (2). It is therefore imperative that the ventilatory transportation practices of a facility be audited frequently.

At Chris Hani Baragwanath Academic Hospital (CHBAH), the multi-disciplinary ICU is located approximately 220 m from the theatre, with an elevator required to transport the patient to either first floor ICU (medical and surgical patients) or second floor ICU (trauma patients). Transportation may take anywhere from 5 – 20 minutes depending on delays at the elevator. There is a lack of portable mechanical ventilators with which to transport the patients from the theatre back to the ICU. The common method of ventilating patients during transport is manual ventilation with MRBs without tidal volume meters. It is not known how well patients are being ventilated while being transported between the theatre and ICU.

4.2 Aim and objectives

4.2.1 Aim

The aim of this study is to evaluate the arterial carbon dioxide ($PaCO_2$) levels of ventilated adult critically ill post-operative patients on arrival in ICU at CHBAH.

4.2.2 Objectives

The primary objectives of this study are to**:**

- estimate the occurrence of sub-optimal ventilation during transportation to ICU
- compare the $PaCO_2$ before leaving the theatre and the $PaCO_2$ on arrival in ICU
- describe the occurrence of hypocarbia and hypercarbia on arrival in ICU
- document adverse events during transportation.

The secondary objectives of this study are to**:**

- compare the change in the other arterial blood gas (ABG) values before leaving the theatre and on arrival in ICU
- compare the difference in $PaCO_2$ before leaving the theatre and the $PaCO_2$ on arrival in ICU between day and night transportation

- compare the difference in $PaCO_2$ before leaving the theatre and the $PaCO_2$ on arrival in ICU between weekday and weekend transportation.

4.3 Research assumptions

The following definitions will be used in this study.

Anaesthetist: is any qualified doctor working in the Department of Anaesthesiology including interns, medical officers, registrars and consultants.

Intern: is a doctor who completed a university degree but is currently undergoing practical training prior to registration with the Health Professionals Council of South Africa an independent practitioner.

Medical officer: is a qualified doctor practising in the Department of Anaesthesiology under specialist supervision**.** Medical officers with more than 10 years of experience are career medical officers and are regarded as consultants.

Registrar: is a qualified doctor who is registered with the Health Professional Council of South Africa as a trainee anaesthetist.

Specialist Anaesthesiologist: A qualified anaesthesiologist who has completed advanced training in anaesthesia in accordance with the requirements of the Fellowship of the College of Anaesthesiologists and is registered with the Health Professions Council of South Africa, as an anaesthesiologist.

Consultant: is an anaesthesiologist or career medical officer.

Adult: is a person 18-years and older.

Child: is a person younger than 18 years.

Carbon dioxide: $PaCO_2$ is inversely proportional to alveolar ventilation (18) and will be used as a marker of the adequacy of ventilation. In this study, a $PaCO_2$ level between 35 – 45 mmHg will be considered normal (19).

Hypocarbia: is a $PaCO_2$ level below 35 mmHg.

Hypercarbia: is a $PaCO_2$ level above 45 mmHg.

Sub-optimal ventilation: any $PaCO_2$ value outside of the normal range described above.

Acidosis: is a blood pH level of less than 7,35.

Alkalosis: is a pH level above 7,45.

Manual resuscitator bag: is a self-inflating bag-valve device used to administer intermittent positive pressure manual ventilation to a patient. It may also be referred to as a self-inflating bag or an AMBU Bag (Artificial Manual Breathing Unit™) (20).

Day: the hours between 8:00 and 16:00.

Night: the hours between 16:01 and 7:59.

Weekday: is Monday from 08:00 to Friday at 16:00.

Weekend: is Friday from 16: 01 to Monday at 07:59.

Adverse event: is “an injury that was caused by medical management (rather than the underlying disease) and that prolonged the hospitalization, produced a disability at the time of discharge, or both” (21).

Acute Respiratory Distress Syndrome: “is an acute onset symmetrical diffuse inflammatory lung injury, leading to increased pulmonary vascular permeability, increased lung weight, and loss of aerated lung tissue with hypoxaemia and bilateral radiographic opacities, associated with increased venous admixture, increased physiological dead space and decreased lung compliance” (3). Severe acute respiratory distress syndrome with a PaO_2/FiO_2 ratio of < 100 will be used as a cut off in this study (22).

4.4 Demarcation of study field

The study will be conducted at CHBAH. CHBAH is a 2888-bed central hospital. The hospital has 21 theatres, which include trauma, obstetrics and gynaecology, emergency, neurology, urology, ophthalmology, orthopaedics, general surgery and

paediatric surgery. On average 65 000 cases are done annually. The general ICU consists of 18 adult beds admitting medical, surgical and trauma patients.

4.5 Ethical considerations

Approval to conduct the study will be obtained from the Human Research Ethics Committee (Medical) and the Graduate Studies Committee of the University of the Witwatersrand. Approval will also be obtained from the CHBAH Medical Advisory Committee (Appendix A), as well as the heads of the departments of Anaesthesiology and ICU (Appendix B).

The analysis of ABG samples in theatre and on admission to ICU is standard practice. Given that the nature of this study involves collecting data from critically ill ICU patients who are intubated and require mechanical ventilation and are being transported from theatre post-operatively to ICU, it will be impractical to attempt to obtain consent pre-emptively from the patient.

Consent to use the data obtained from the ABG analysis will be requested from the patients' family members and an information letter (Appendix C) will be given to them. This will be done by approaching the family member and explaining the study, its purpose and how it was conducted, and then requesting them to allow their family member's data to be included in the study. If they agree, they will be asked to sign a consent form (Appendix D). Secondly, this study will make use of deferred patient consent due to the likelihood of the patients being incapacitated at the time of data collection. Once the patient is awake and able to comprehend, to agree, and to sign a consent form, consent will be obtained from the patient. The study and its purpose, as well as their involvement, will be explained to the patient, they will be informed that their data has already been collected and they will be asked for consent to include this data as part of the study. If they agree, they will be given a patient information letter (Appendix E) and asked to sign a consent form (Appendix D).

In the event of the patient's death or continued incapacity prior to consent being obtained from them, the family's consent will be used. In the event that the family refuse to give consent and the patient, upon awakening, agrees to participate in the study, the patient's consent will override the refusal of the family. Patients and

their family members who do not agree to take part in the study will have their data excluded.

Confidentiality will be maintained by collecting data without identifying information. A separate list of patient name, hospital number and study number will be generated and filed separately. Patients' data information sheets will be allocated a study number. Only the researcher and supervisors will have access to raw data.

Any abnormality in the initial ABG will be reported to the attending doctor. Should the results of the study indicate that, ventilation via an MRB is sub-optimal, this will be reported to the Head of the Department of Anaesthesiology.

Raw data will be stored securely for six years after the completion of the study in a locked cupboard. Electronic data will be stored securely in a password-protected database.

The study will be conducted according to the principles of the Declaration of Helsinki (23) and the South African Guidelines for Good Clinical Practice (24).

4.6 Research methodology

4.6.1 Research design

A prospective, cross-sectional, contextual descriptive research design will be followed in this study.

Prospective studies are designed to begin with an examination of a presumed cause, and then measure the presumed effect or outcome (25). This study is prospective because the researchers will begin by measuring a cause, for example bag-ventilation and its effect on $PaCO_2$ levels, to assess the adequacy of manual ventilation in the population described.

Cross sectional studies are those in which data is obtained at a single point in time amongst diverse participants as opposed to multiple data obtained from the same participants at different time periods (25).

Contextual studies are defined as those that are concerned with understanding the circumstances, environmental and holistic context within which the study problem

is associated (26). This is a study that is contextual to patients arriving at ICU from theatre at CHBAH.

Descriptive studies are defined by Brink et al. (25) as “Research studies in which phenomena are described, or the relationship between variables is examined; No attempt is made to determine cause-and-effect relationships”. This study is descriptive because it is examining the relationship between manual ventilation and $PaCO_2$ levels.

4.6.2 Study population

The study population consists of all intubated patients arriving in ICU from theatre at CHBAH.

4.6.3 Study sample

Sample size

The sample size was determined in consultation with a biostatistician using EpiInfo version 7.2.0.1 which was based on a South African study by De Vasconcellos et al. (1) where the frequency of low saturation, possibly indicating inadequate ventilation, of patients on arrival in ICU was 15.5%. Assuming a total population of 60 critically ill intubated and ventilated patients being transported from theatre to ICU per month with a 5% margin of error, at a 95% confidence level, a minimum sample size of 46 patients was estimated to have a minimum power of 80%.

Sampling method

In this study, a convenience sampling method will be used. Convenience sampling is a non-probability sampling procedure that involves the selection of the most readily accessible people for the study (25).

Inclusion and exclusion criteria

The inclusion criteria for this study are:

- patients transported from theatre to ICU post-operatively
- who are intubated or who have a tracheostomy in situ

- who are being manually ventilated with an MRB
- who have an arterial line in situ
- for whom consent has been obtained.

The exclusion criteria in this study are:

- patients younger than 18 years of age
- patients with severe acute respiratory distress syndrome.

4.6.4 Data collection

Data collection sheet

A draft data collection sheet (Appendix F) was compiled and given to three senior anaesthesiologists to review for face and content validity. The suggestions made were incorporated into the final data collection sheet. The following information will be collected:

- study number
- date and day
- transport time
- demographics (age, sex, surgical procedure)
- pre-transport ABG in theatre
- post-transport ABG on arrival in ICU
- drugs administered for transport and doses (sedative/opioid/neuromuscular blocker)
- full manual ventilation or partial ventilation (where the patient is spontaneously breathing and their ventilation is being supported by assisted manual breaths administered by the anaesthetist)
- MRB and peep

- any adverse events occurring.

Data collection

The researcher will identify the ICU patients who are scheduled to be transported to the theatre for operations, either emergency or elective, or scheduled to be admitted to the ICU post-operatively, from the booking information available in theatre and ICU.

The pre-transport ABG sample will be collected by the anaesthetist conducting the case, from the patient's arterial line, before the patient is disconnected from the ventilator in theatre. The post-transport ABG will be collected by the researcher immediately on arrival in the ICU before the patient is attached to the ICU ventilator. The ABG sample will be collected and analysed in a standardised manner. The pre-transport ABG and the post-transport ABG will be analysed using a single automated blood gas analysis machine (Radiometer ABL800 Basic) within 10 minutes of collection (19) as per standard practice. If the ABG is unable to be analysed within the 10-minute window, the sample will be capped and put on ice to maintain the sample integrity until the first opportunity to analyse the sample arises. Should the sample be unable to be analysed within 30 minutes of collection, the sample will be discarded and the patient's data excluded from the study.

The researcher will allocate a study number to the data collection sheet that will correspond to the patient. The values of the ABG analysis will be captured onto the data collection sheet. The data collection sheet will then be completed using the patient's record. The data will be collected by the researcher and by the doctors rotating in ICU when the researcher is not personally available. This information will be securely stored until consent can be obtained from either the patient or their family members. In the event of refusal of consent, the data will be destroyed.

In critically ill patients, premorbid conditions or decompensations necessitating ICU admission may have an impact on ventilation. Conditions such as obesity hypoventilation syndrome (27) or chronic obstructive pulmonary disease (28) may cause a spontaneously breathing patient to have chronically elevated $PaCO_2$

levels and conversely, a patient who is in pain (29), or who has a metabolic acidosis (30) from any cause, may be hyperventilating and thus have a low $PaCO_2$ level. While it is important to bear in mind the impact premorbid conditions may have on ventilation, this study is focusing on patients who are being manually ventilated by an anaesthetist during transport from theatre to ICU. The possible change in the $PaCO_2$ levels on arrival in ICU will be a marker of the adequacy of ventilation provided by the anaesthetist using the MRB bag during transportation regardless of their underlying conditions.

There may be other causes of altered $PaCO_2$ levels in ICU patients other than ventilation. These may include cardiorespiratory abnormalities, which may be the primary reason for admission into the ICU or may develop subsequently as a result of ongoing physiologic derangements. Of these, ARDS (22) has the greatest effect on ABG values. Patients with severe ARDS (22) will be excluded from the study.

4.6.5 Data analysis

A Microsoft Excel spreadsheet will be used to capture data. Data will be analysed in consultation with a biostatistician using STATA version 15 (StataCorp, USA). Descriptive and inferential statistics will be used. Categorical variables will be described using numbers and percentages and continuous variables using means and standard deviations, or medians and interquartile ranges, depending on the distribution of the data. All continuous variables will be compared using paired t-tests or the Wilcoxon matched pairs. A p-value of < 0.05 will be considered statistically significant.

4.7 Significance of the study

The hazards of transporting critically ill patients with the use of MRBs has been demonstrated internationally (5, 13) and nationally (1), even during short transportation times (5, 31).

This study is necessary because it will provide empirical evidence of the possible sub-optimal patient ventilation from theatre to ICU in the local context. The results of the study will indicate the prevalence of hypercarbia and hypocarbia in patients

arriving at ICU from theatre. Factors that could account for differences in patient ventilation may be identified during the study. The study could also be used to motivate for the use of portable mechanical ventilators during the transport of patients from theatre to ICU if ventilation with MRBs is found to be sub-optimal.

4.8 Validity and reliability of the study

Reliability is defined by Botma et al. (32) as “Whether the conclusions of a study are justified based on the design and interpretation” and reliability as “ the consistency of the measure achieved” (32). In this study, validity and reliability will be ensured by the following:

- using an appropriate study design and methodology
- analysing the ABG sample within a 10-minute window (19)
- capping the sample and storing it on ice if unable to asses within the 10-minute window
- discarding samples that have not been assessed within 30 minutes
- using a single automated blood gas analyser which is calibrated
- analysing the data in consultation with a biostatistician.

4.9 Potential limitations

- contextual design; the research results may not be generalisable to other contexts
- convenience sampling; the population may be over or under represented in the available sample
- confounding factors; respiratory and cardiopulmonary derangements in physiology are common in critically ill patients and may influence the ventilatory parameters and thereby the $PaCO_2$ level

- anaesthetists may become aware of the study and may alter their technique of manual ventilation to try to produce a more acceptable result.

4.10 Project outline

4.10.1 Time frame

Activity	June 2018	Sep 2018	Oct 2018	Nov 2018	Jan 2019	Feb 2019	Mar 2019	Apr 2019
Proposal preparation								
Literature review								
Proposal submission								
Ethics and post-graduate approval								
Data collection								
Data analysis								
Writing article								
Submission								

4.10.2 Budget

Description	Price per item	Number of Items	Total
Proposal	R1/page	210	R210
Data collection sheet, consent and patient information sheet	R1/page	300	R300
Ethics and post-graduate application forms	R1/page	256	R256
Research report	R1/page	400	R400
Binding	R200/copy	3	R800
Total			R1966

The Wits Department of Anaesthesiology will incur the costs of paper and printing.

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4.12 Appendices

Appendix A: Permission letter from the Medical Advisory Committee CHBAH

Ferndale

2194

21 June 2018

To the Medical Committee Chris Hani Baragwanath Academic Hospital

Dear Chairperson

Approval for M Med research

My name is Mulai Slave and I am currently a registrar in the Department of Anaesthesiology. I would like to do a study with the title: Carbon dioxide levels of ventilated adult critically ill post-operative patients on arrival to the intensive care unit.

The aim of the study is to determine if the use of manual ventilation by anaesthetists during the transportation of critically ill intensive care unit patients results in a change in their arterial carbon dioxide levels, a marker of the adequacy of ventilation.

The study will not alter patient management and confidentiality of the participants will be maintained at all times.

I would like to request permission to investigate the objectives of the research proposal. There will be no cost to the hospital during the course of the study.

Ethical clearance (clearance number M180779) and Graduate Studies Committee approval have been obtained.

I have attached a copy of my proposal for your perusal.

I thank you in advance

Mulai Slave

0825104800

mulai@hotmail.co.uk

Appendix B: Permission letters from the heads of departments of anaesthesiology and Intensive care unit

WITS UNIVERSITY

DEPARTMENT OF ANAESTHESIOLOGY
UNIVERSITY OF THE WITWATERSRAND,
JOHANNESBURG
Tel.(011)933-9334/5 / Fax (011)933-1843

FACULTY OF HEALTH SCIENCES

28 July 2018

Ms Zanele Ndlovu
Administrative Officer
Human Research Ethics (Medical)

RE : DR M.L SLAVE STUDENT NUMBER 0701846E

I herewith grant permission to Dr Mulai Slave to conduct the study titled "Carbon dioxide levels of ventilated adult critically ill post-operative patients on arrival to the intensive care unit". This will entail recording the arterial blood gas carbon dioxide levels of patients when they leave theatre and when they arrive in ICU.
With Kind Regards

Yours sincerely

DR D LINES
PRNCIPAL SPECIALIST AND ACTING HEAD
OF DEPARTMENT OF ANAESTHESIA
UNIVERSITY OF THE WITWATERSRAND

215 Sun village

374 York Avenue

Ferndale

2194

27 June 2018

To the Head of the Intensive Care Unit Chris Hani Baragwanath Academic Hospital

Dear Prof Mathivha

Approval for M Med research

My name is Mulai Slave and I am currently a registrar in the Department of Anaesthesiology. I would like to do a study with the title: Carbon dioxide levels of ventilated adult critically ill post-operative patients on arrival to the intensive care unit.

The aim of the study is to determine if the use of manual ventilation by anaesthetists during the transportation of critically ill intensive care unit patients results in a change in their arterial carbon dioxide levels, a marker of the adequacy of ventilation.

The study will not alter patient management and confidentiality will be maintained at all times.

I would like to request permission to investigate the objectives of the research proposal. There will be no cost to the hospital during the course of the study.

Ethical clearance and graduate studies committee approval will be obtained.

I have attached a copy of my proposal for your perusal.

I thank you in advance

Mulai Slave

0825104800

mulai@hotmail.co.uk

Approved/Not Approved

Name and Title Prof L.R. Mathivha

Signature

Date 10/7/2018

Appendix C: Family information sheet

Dear Family Member

Hello, my name is Dr Mulai Slave, I am a doctor in the Department of Anaesthesiology. As part of my training I am doing a research study and would like to invite your family member to be part of this study. My study is titled: Carbon dioxide levels of ventilated adult critically ill post-operative patients on arrival in the intensive care unit.

When very ill patients come back from their operation, the doctor who made sure they were asleep and had no pain during the operation, helps them breathe using a special breathing bag. My study will be looking at how the doctor is using the special breathing bag to help the patient breathe. To do this I will be looking at blood tests that are always taken from very sick patients before the patient leaves theatre and immediately on arrival in the ICU. These tests are called the ABG. The blood is taken from a drip and your family member was not pricked to get it. I am asking you if I may use the ABG results for my study.

Once your family member is awake, we will ask them if they are happy to be a part of my study. Should you or your family member not want to take part in this study, or want to withdraw, the treatment they receive will not change in any way.

This study will not directly benefit your family member, however, knowing how the doctor uses the special breathing bag could help very ill patients in the future.

We will keep the information we collect from your family member confidential, meaning no one else will know who the patient is or see the results of the blood tests. There will be no name or other identifying information with the blood tests, only a study number.

Before you give permission to include your family member in this study please make sure that you understand what the study involves.

Should you have any questions please feel free to ask me personally or email me at 0701846E@students.wits.ac.za or to contact Professor CB Penny, Chairperson of the Human Research Ethics Committee (Medical) at the University of Witwatersrand, on telephone no. 011 717 2301.

Thank you for taking the time to read this letter.

Yours sincerely

Dr Mulai Slave

Appendix D: Consent form

PARTICIPANT CONSENT SHEET

Carbon dioxide levels of ventilated adult critically ill post-operative patients on arrival in the intensive care unit

1. I have been given a Participant Information Sheet which explains the nature and processes involved in this study, which is attached hereto;
2. I was given time to read it, or had it read to me, in the language I best understand;
3. I was given time to ask any questions I wanted to and found any answers given to me to be reasonable and satisfactory;
4. I believe I fully understand why the study is being conducted and what the intended outcomes will be;
5. I understand that there will be no immediate benefit to me, should I agree to participate, nor will I receive any payment; conversely, participation will not cost me anything but my time;
6. I understand that, even if I initially consent to take part in the study, I may subsequently withdraw at any time and would not be required to give any reasons; if that happened, any data collected about me for the purposes of the study would immediately be destroyed, unless I give consent for it to be retained
7. I have been given a range of contact details, listed below. If I require further information or become concerned about any aspect of this study I am free to speak to any of these contacts.

Contact details:

M.L Slave, Principal Investigator, telephone no. 0119339334 or by e-mail at 0701846E@students.wits.ac.za

Professor CB Penny, Chairperson of the Human Research Ethics Committee (Medical) at the University of Witwatersrand, on telephone no. 011 717 2301, or by e-mail at Clement.Penny@wits.ac.za.

Ms. Z Ndlovu or Mr Rhulani Mkansi, Committee Secretariat, telephone nos.: 011 717 2700 or 1234, or by e-mail at: Zanele.Ndlovu@wits.ac.za or Rhulani.Mkansi@wits.ac.za

Name of Participant: _____

Name of Family Member _____

Relationship to patient _____

Date: _____

Place: _____

Signature or mark _____

Witnessed by:

Name of Witness: _____

Signature: _____

Date: _____

Appendix E: Patient information sheet

Dear Patient

Hello, my name is Dr Mulai Slave, I am a doctor in the Department of Anaesthesiology. As part of my training I am doing a research study and would like to invite you to be part of this study. My study is titled: Carbon dioxide levels of ventilated adult critically ill post-operative patients on arrival in the intensive care unit.

When very ill patients come back from their operation, the doctor who made sure they were asleep and had no pain during the operation helps them breathe using a special breathing bag. My study will be looking at how the doctor is using the special breathing bag to help the patient breathe. To do this I will be looking at blood tests that are always taken from very sick patients before the patient leaves theatre and immediately on arrival in the ICU. These tests are called the ABG. The blood was taken from a drip and you were not pricked to get it. I am asking you if I may use the ABG results for my study.

Permission to include you in this study has already been requested from your family member whilst you were asleep. Now that you are awake, I would like to invite you to be a part of my study. Should you not want to take part, or want to withdraw, the treatment you receive will not change in any way.

This study will not directly benefit you, however, knowing how the doctor uses the special breathing bag could help very ill patients in the future.

We will keep the information we collect from you confidential, meaning no one else will know who you are or see the results of the blood tests. There will be no name or other identifying information with the blood tests, only a study number.

Before you give permission to be included in this study please make sure that you understand what the study involves.

Should you have any questions please feel free to ask me personally or email me at 0701846E@students.wits.ac.za or to contact Professor CB Penny, Chairperson of the Human Research Ethics Committee (Medical) at the University of Witwatersrand, on telephone no. 011 717 2301.

Thank you for taking the time to read this letter.

Yours sincerely

Dr Mulai Slave

Appendix F: Data collection sheet

Please tick

STUDY NO								
Date		**Mon**	**Tues**	**Wed**	**Thur**	**Fri**	**Sat**	**Sun**
Time of leaving theatre		**Time of arrival in ICU**						
Demographics		**Age**				**Male**	**Female**	
Procedure done								
Partially or fully ventilated?		**Partial**				**Full**		
Drugs administered for transport		**Sedatives**	**opioids**			**Neuro-muscular blockers**	**Other**	
Drug and dose								
MRB bag		**No PEEP**				**PEEP level**		
Pre-transport ABG in THEATRE		**Post-transport ABG in ICU**						
FiO_2		**FiO_2**				**1**		
pH		**pH**						
PaO_2		**PaO_2**						
$PaCO_2$		**$PaCO_2$**						
Lactate		**Lactate**						
Base excess		**Base excess**						
HCO_3		**HCO_3**						
SaO_2		**SaO_2**						
Any adverse event occurring during transportation?			**Yes**			**No**		
If Yes, specify:								

Section 5: Annexures

5.1 Ethics approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Mulai Slave et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180779

NAME: (Principal Investigator)	Dr Mulai Slave et al
DEPARTMENT:	Anaesthesiology Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Carbon dioxide levels of ventilated adult critically ill post-operative patients on arrival to the intesive care unit
DATE CONSIDERED:	27/07/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Juan Scribante
APPROVED BY:	Doctor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	15/01/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **July** and will therefore be due in the month of **July** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

19/01/2019
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

5.2 Graduate studies approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

04 January 2019
Person No: 0701846E
PAG

Dr MLD Slave
215 Sunvillage
374 Yonc Ave
Femdale
2194
South Africa

Dear Dr Mulai Slave

Master of Medicine in Anaesthesia: Approval of Title

We have pleasure in advising that your proposal entitled *Carbon dioxide levels of ventilated adult critically ill post-operative patients on arrival to the intensive care unit* 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

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

5.3 Medical Advisory Committee approval

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 11 December 2018

TITLE OF PROJECT:

Carbon dioxide levels of ventilated adult critically ill postoperative patients on arrival to the Intensive care unit.

UNIVERSITY: Witwatersrand

Principal Investigator: Mulai Slave

Department: Anaesthesiology

Supervisor : Juan Scribante

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is 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.

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Recommended
(On behalf of the MAC)
Date: 11/12/2018

.....
Approved/Not Approved
Hospital Management
Date: 12/12/2018

5.4 Turnitin report

11 December 2020

The Chairperson
Graduate Studies Committee
Faculty of Health Sciences
University of the Witwatersrand

Dear Professor Papathanasopoulos

Re: M Med: **Carbon dioxide levels of ventilated adult critically ill post-operative patients on arrival to the intensive care unit**

Dr Mulai Slave, student number: **0701846E**, has submitted her research report to Turnitin which revealed a similarity index of 12%. These similarities appear not to be plagiarism but mainly the use of common terminology and phrases specific to the topic of the research.

Yours sincerely,

Juan Scribante
Supervisor

0701846e:turnitin_version.docx

ORIGINALITY REPORT

12%	7%	9%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Yi-Chen Lai. "1: ACTIVATION OF POLY(ADP-RIBOSE) POLYMERASE-1 CONTRIBUTES TO NAD+ DEPLETION AND IMPAIRED NAD+ DEPENDENT MITOCHONDRIAL RESPIRATION FOLLOWING STATUS EPILEPTICUS :", Critical Care Medicine, 12/2011 Publication	1%
2	"ESICM LIVES 2017", Intensive Care Medicine Experimental, 2017 Publication	1%
3	Submitted to University of Witwatersrand Student Paper	1%
4	www.ncbi.nlm.nih.gov Internet Source	<1%
5	www.tandfonline.com Internet Source	<1%
6	Osman Bastug, Tamer Gunes, Levent Korkmaz, Ferhan Elmali, Fatma Kucuk, Mehmet Adnan Ozturk, Selim Kurtoglu. "An evaluation of intra-	<1%