MESSAGE FROM THE EDITOR-IN-CHIEF / MESSAGE DU RÉDACTEUR EN CHEF

Responding to Ebola: The role of medical journals during global public health emergencies / Réagir au virus Ebola : le rôle des revues médicales pendant les urgences mondiales de santé publique

COMMENTARY

The OSCILLATE trial: Implications for respiratory therapists then and now

EDITORIAL

Surfactant: The importance of documented policy and procedure

ORIGINAL ARTICLE

Prediction of endotracheal intubation outcome in opioid-poisoned patients: A clinical approach to bispectral monitoring

REVIEWS

To PAPR or not to PAPR?

Surfactant administration in neonates: A review of delivery methods
INTRODUCING TUDORZA® GENUAIR®
A new LAMA in COPD*

Imagine the possibilities

TUDORZA GENUAIR demonstrated a statistically significant improvement in lung function (morning pre-dose [trough] FEV₁) at 24 weeks vs. placebo (TUDORZA GENUAIR 400 mcg BID, 55 mL vs. placebo, -73 mL, p<0.0001)²,³†

Indications and clinical use:
TUDORZA GENUAIR (aclidinium bromide) is indicated as a long-term maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

- TUDORZA GENUAIR is not indicated for the relief of an acute deterioration of COPD
- Indicated in patients >18 years of age

Other relevant warnings and precautions:
- Should not be used for the initial treatment of acute episodes of bronchospasm (i.e., as rescue therapy)
- Should not be initiated in patients with acutely deteriorating COPD
- Should not be used more often or at higher doses than recommended
- Should not be used more frequently than twice daily
- Patients who have been taking inhaled, short-acting bronchodilators on a regular basis should start using them only for symptomatic relief; patients not on a short-acting bronchodilator should be provided one for symptomatic relief of acute symptoms
- Worsening of narrow-angle glaucoma
- Worsening of urinary retention
- Immediate hypersensitivity reactions; patients with a history of hypersensitivity reactions to atropine should be closely monitored
- Paradoxical bronchospasm
- Use with caution in patients with certain cardiovascular conditions

Occurrence of headache or blurred vision may influence the ability to drive or use machinery

For more information:
Please consult the Product Monograph at http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp for important information relating to adverse reactions, drug interactions, and dosing information, which have not been discussed in this piece.

The Product Monograph is also available on request by calling 1-800-957-7679. For the complete Formulary listing, please visit the Ontario Drug Benefit website at: http://www. health.gov.on.ca/en/public/programs/drugs/ programs/odb/odb.aspx

* LAMA: Long-Acting Muscarinic Antagonist; COPD: Chronic Obstructive Pulmonary Disease.
† A randomized, double-blind, placebo-controlled, 24-week study in patients aged ≥40 years (N=819) with a clinical diagnosis of stable moderate-to-severe COPD (post-bronchodilator FEV₁ of ≥30% to <80% of predicted normal value) and a history of smoking of at least 10 pack-years. Morning trough (pre-dose) FEV₁ was defined as FEV₁ measured 12 hours after the previous evening dose of TUDORZA GENUAIR.

THE FAMILY OF COMPACT ICU VENTILATORS

High Performance Capabilities for Any Environment

Presenting ventilators from Hamilton Medical
Intelligent Ventilation Solution from ICU to MRI

BOMImed
Better Answers for Better Care

CANADA
96 TERRACON PLACE
WINNIPEG, MB
R2J 4G7

USA
844 EAGLE DRIVE
BENGENVILLE, IL
60106

GENERAL INQUIRIES
T. 800.667.6276
F. 877.435.6984
E. info@bomimed.com

www.bomimed.com
Boehringer Ingelheim
Respimat
Responding to Ebola: The role of medical journals during global public health emergencies / Réagir au virus Ebola : le rôle des revues médicales pendant les urgences mondiales de santé publique
Jason Nickerson

The OSCILLATE trial: Implications for respiratory therapists then and now
Lori Hand

Surfactant: The importance of documented policy and procedure
Ron Valotaire

Prediction of endotracheal intubation outcome in opioid-poisoned patients: A clinical approach to bispectral monitoring
Nastaran Eizadi-Mood, Ahmad Yaraghi, Mahsa Alikhasi, Mitra Jabalameli, Shadi Farsaei, Ali Mohammad Sabzghahabae
Over the past few decades, opioid toxicity and overdose, often leading to death, have emerged as serious problems in many countries. In fact, the number of deaths resulting from opiate overdose have exceeded murder rates in some metropolitan centres in the Unites States. A hallmark of opioid toxicity is respiratory depression, a condition that, in many cases, requires endotracheal intubation to mitigate the risk of hypoxemia when opioid antagonists fail to produce an adequate response. Given the importance of the decision, several indexes have been developed to guide clinicians in determining the need for intubation to avoid 'crash' airway scenarios. This observational study investigated the utility of the bispectral index in a population of opioid-poisoned patients who were admitted to a major referral centre for toxicological emergencies in central Iran.

To PAPR or not to PAPR?
Vanessa Roberts
The current outbreak of Ebola virus in Northeastern Africa has prompted clinicians and health care workers to revisit the issue of infection prevention and control procedures, especially with regard to personal protective equipment (PPE). After an introductory review of Ebola routes of transmission, this article compares and contrasts the advantages and disadvantages of powered air-purifying respirators versus N-95 masks, particularly with respect to aerosol-generating procedures. Additionally, the authors describe their experience with PPE measures and policies at the Jewish General Hospital in Montreal, Quebec. Given the frontline responsibility of respiratory therapists in treating individuals with communicable infections, the authors stress the importance of being proactive in the decision-making process for PPE use and implementation.

Surfactant administration in neonates: A review of delivery methods
Nina Nouraeyan, Alicia Lambrinakos-Raymond, Marisa Leone, Guilherme Sant'Anna
Despite the enormous success and widespread use of surfactant for the treatment of neonatal respiratory distress syndrome, optimal delivery methods for its administration in preterm infants remain unclear. Although substantial advances in respiratory care have occurred since early studies investigating this topic were published, the literature remains limited, and is often conflicting and dated. This review discusses several important aspects of surfactant administration, ventilation strategies and other key considerations. The authors also provide a detailed protocol for surfactant administration used at the McGill University Health Centre in Montreal, Quebec.

Calendar of Events

Advertisers’ Index
When a patient is recovering, who knows better when and how much ventilator support a patient needs than the patient themselves?

The Servo-U, including Nava software, lets the patient’s own physiologic respiratory signal control the timing and amount of support for every breath.

The same signal provides valuable insight into the patient’s respiratory drive, giving clinicians an indispensable tool for diagnostics and weaning.

Give the patient what they need to breathe easier and the clinicians what they need to understand the patient’s respiratory condition - with Servo-U and NAVA.

MAQUET — The Gold Standard.
Responding to Ebola: The role of medical journals during global public health emergencies

As a researcher in global public health and a clinician in a high-income, well-resourced health system, I have had the opportunity to work across a spectrum of health services, ranging from the treatment of neglected tropical diseases to providing care for routine surgical pathologies. Regrettably, the focus of the global health care architecture that predominates the research and development agendas around the world has adopted a focus that is frequently out of line with the needs of the poor, resulting in too little attention and innovation being devoted to pressing global health problems (1). On occasion, however, an emerging health concern propels tropical diseases to the forefront of medical practice in Canada or elsewhere, prompting us to reconsider our vulnerabilities within an increasingly globalized world.

Presently, health systems around the world are preparing for the potential of arrival of patients who may have been exposed to the Ebola virus disease by way of an outbreak that began in Guinea in December 2013, but was only declared in March, and has since spread to Liberia, Sierra Leone and Nigeria (2). At press time, the case fatality rate of the outbreak was 54.9%, with a cumulative total of 2,240 cases and 1,229 deaths, and no indications of a resolution to this epidemic (3).

Control of the virus is proving to be difficult for several reasons (4). The geographical spread of cases in and between the countries affected presents a major logistical challenge in identifying and tracing individuals who may have been exposed to the virus. While much attention has been given to the development of new drugs for the treatment of Ebola, less attention has been devoted to the role of strong health systems in identifying, controlling and responding to the epidemic. Regrettably, the health systems of the affected countries face major longstanding challenges, including severe shortages of health workers. In resource-constrained settings, access to even basic primary care is poor and often hampered by systemic problems such as access to essential medicines, effective health information systems for monitoring disease trends and patterns, and the application of evidence-based treatments, making the effective detection, control and treatment of a complex disease, such as Ebola, extremely challenging.

In Canada, the Ebola outbreak continues to be at the forefront of public discussion and of concern to health workers across the country, perhaps, in part, prompted by the infection of several American and European aid workers. In the current issue of the Journal, for example, we present a brief review (pages 87-90) on one hospital’s infection control procedures that are in place for precisely a situation such as this. The commentary highlights the challenges imposed on Canadian health facilities to identify best practices for high-risk, low-probability scenarios, and to ensure that we can continue to provide treatment in a manner that is effective and vigilant.

Correspondence: Dr Jason Nickerson, Bruyère Research Institute, 308B–85 Primrose Avenue, Ottawa, Ontario K1R 7G5.
Telephone 613-562-6262, e-mail editor@csrt.com

Réagir au virus Ebola : le rôle des revues médicales pendant les urgences mondiales de santé publique

En qualité de chercheur en santé publique mondiale et de clinicien dans un système de santé riche et bien doté en ressources, j’ai eu la chance de travailler dans divers services de santé, du traitement de maladies tropicales négligées aux soins de pathologies chirurgicales courantes. Malheureusement, les programmes de recherche-développement du monde entier sont surtout tournés vers des sujets très éloignés des besoins des pauvres. Par conséquent, on porte très peu attention aux problèmes de santé mondiaux pressants, et les innovations les visent rarement (1). Il arrive toutefois qu’une préoccupation de santé émergente propulse les maladies tropicales à l’avant-plan de l’exercice de la médecine au Canada ou ailleurs, nous incitant à réévaluer nos vulnérabilités dans un milieu de plus en plus mondialisé.

Les systèmes de santé du monde entier se préparent à l’arrivée potentielle de patients susceptibles d’avoir été exposés au virus Ebola par suite d’une écllosion qui s’est manifestée en Guinée en décembre 2013, mais qui a seulement été déclarée en mars et qui s’est répandue au Liberia, en Sierra Leone et au Nigeria depuis (2). Au moment de mettre sous presse, le taux de mortalité de cette écllosion s’élevait à 54,9 %, pour un total cumulatif de 2 240 cas et 1 229 décès, sans que rien n’en indique la résolution (3).

Il est difficile de contrôler le virus pour plusieurs raisons (4). La dispersion géographique des cas dans les pays concernés et d’un pays à l’autre représente un immense défi logistique pour dépister et retracer les cas d’exposition éventuelle au virus. On s’est beaucoup intéressé au développement de nouveaux médicaments pour traiter le virus Ebola, mais beaucoup moins au rôle de solides systèmes de santé pour dépister et contrôler l’épidémie ainsi que pour y réagir. Malheureusement, de graves problèmes grèvent depuis longtemps les systèmes de santé des pays touchés, y compris d’importantes pénuries de travailleurs de la santé. Dans des milieux pauvres en ressources, il est difficile d’accéder à de simples soins de première ligne. Les soins de base sont souvent entravés par des problèmes systémiques comme la pénurie de médicaments essentiels, l’absence de systèmes d’information efficaces sur la santé pour surveiller les tendances et les profils des maladies et la difficulté à mettre en œuvre des traitements fondés sur des données probantes. Ces obstacles compliquent énormément le dépistage, le contrôle et le traitement efficace de maladies complexes comme le virus Ebola.

Au Canada, l’écllosion du virus Ebola continue d’être au cœur des discussions publiques et des préoccupations des travailleurs de la santé, peut-être en partie à cause de l’infection de quelques travailleurs humanitaires américains et européens. Dans le présent numéro du Journal, par exemple, nous présentons un bref commentaire (pages 87-90) sur le protocole de contrôle des infections d’un hôpital, créé...
Despite this heightened awareness and preparations, several experts have noted that the risk of an Ebola epidemic in Canada is likely low. Unsurprisingly, the justification of this reasoned call is not because Canada harbours an effective drug for Ebola, but rather because Canada’s health care system is well-equipped to effectively deal with a disease outbreak such as this. Case definitions have been established, infection control protocols are in place and our public health surveillance system is strong. Rather than being a call for complacency, the statement that our risk of an epidemic is low is, in fact, a call to arms to ensure that all health professionals are aware of how to safely care for a patient with a highly communicable disease such as Ebola, and that necessary equipment, policies and protocols are in place to be immediately put into action.

Beyond the challenges of clinical care, disease epidemics, such as Ebola, severe acute respiratory syndrome or H1N1, present major intellectual challenges for health professionals who must care for patients for whom there is a small or no evidence base to guide treatments. Ebola has rarely been treated outside of a handful of resource-poor countries where access to critical care medicine is poor; it is, therefore, conceivable that with stronger resources, greater reductions in mortality could be achieved. At the same time, this also means that clinicians are largely starting anew to build the evidence base on which future treatment guidelines and protocols ought to be based. This is where academic medicine, including clinician-investigators and authors, as well as peer-reviewed journals such as ours, must play a strong role in advancing the science of global health. As clinicians with access to resources to provide comprehensive interventions to patients with rare or neglected diseases, and the ability to report on our successes and failures in doing so, we have a responsibility to share these experiences so that others may build on them.

Respiratory therapists play a leading role in the frontline care of critically ill patients, including making important decisions concerning the processes and systems that ought to be in place to ensure that Canadian health care facilities can safely care for patients with diseases such as Ebola. By sharing these experiences in forums that are accessible to other clinicians in low- and middle-income countries, and providing those clinicians with an opportunity to share their experiences with us, this is a direct opportunity to influence the organization and delivery of care globally, and is an opportunity that we all must embrace.

JASON NICKERSON  RRT  FCSRT  PH.D.
EDITOR-IN-CHIEF

REFERENCES

JASON NICKERSON  RRT  FCSRT  PH.D.
REDACTEUR EN CHEF

RÉFÉRENCES
WILAmed AIRcon Respiratory Humidifier
Complete respiratory humidification for all patient groups

The high-performance WILAmed AIRcon Respiratory Humidifier combines modern technology and innovative design. It is suitable for a wide range of clinical applications needing humidified high-flow oxygen therapy for invasive and non-invasive ventilation.

**Humidification Redefined**
- Suitable for all common neonatal to adult ventilators
- Protection Class II for clinical and extra-clinical use
- 3 function modes (IV, NIV, FREE)
- Extended accessory range
- Elaborated alarm management
- Automatic water level monitoring
- Incident and alarm protocol (data exportable to PC)
- Low maintenance with no hidden costs
- Economical energy consumption

**Easy to use**
- 3.5” TFT colour display with automatic dimmer
- Logical menu navigation with symbols and pictograms
- Treatment pause function
- Expiratory tube: adjustable heating performance
- Individual adjustment of humidification performance

Aircon™ is a trademark owned by WILAmed GmbH

For more information contact:
Christy-Ann Zunti, RRT
Christy-ann.zunti@cardinalhealth.ca
Tel: 604.369.6320
The OSCILLATE trial: Implications for respiratory therapists then and now

Lori Hand BS: RRT CHT CCRA

Acute respiratory distress syndrome (ARDS) continues to be associated with a high mortality rate, ranging from 26% to 28% (1,2). Many survivors experience long-term complications following discharge from hospital (3). Early randomized controlled trials (RCTs) investigating the use of high-frequency oscillatory ventilation (HFOV) in ARDS compared conventional mechanical ventilation (CV) with HFOV. Although these trials showed a potential reduction in mortality with HFOV, the strategies that were used in the CV protocols are not currently considered to be lung protective (4,5). In addition, small sample sizes were used in these trials (6,7), which may have impacted the generalizability of the results to a broader ARDS population, and introduced potential misrepresentation and bias. Recently, a larger RCT of HFOV versus CV for early ARDS was conducted, and results contrasted those of earlier trials showing that HFOV failed to improve mortality in ARDS (8). These results now cause critical care clinicians caring for ARDS patients to question what modality of mechanical ventilation to use during the late phase of ARDS.

The Oscillation for Acute Respiratory Distress Syndrome (ARDS) Treated Early (OSCILLATE) trial was undertaken to evaluate the effect of early initiation of HFOV on all-cause mortality in adults with moderate to severe ARDS. The study involved a multicentre RCT in five countries (Canada, United States, Chile, Saudi Arabia and India), engaging 39 intensive care units with the goal of enrolling a larger target sample size and using a more lung-protective strategy than previous trials (8). To date, the OSCILLATE trial is the sole RCT of HFOV in ARDS that has enrolled a large number of patients and provided up-to-date, protocolized lung-protective ventilation. The pilot phase of the trial was conducted from July 2007 to June 2008, and the main trial from July 2009 to August 2012. Five hundred forty-eight of the planned 1200 patients were randomly assigned to receive either HFOV following a lung-protective protocol of high set frequency coupled with a prescribed high maximum power and lung recruitment manoeuvres (8-11), or CV using a lung-protective strategy of low tidal volume, high positive end-expiratory pressure and lung-recruitment manoeuvres modelled after the experimental arm of the Lung Open Ventilation Study (12). On recommendation of the data monitoring committee, the trial was stopped early because interim analysis revealed no decrease in mortality with HFOV – and perhaps a tendency toward harm.

Because the OSCILLATE trial compared two mechanical ventilation strategies, involvement of and reliance on respiratory therapists (RTs) was of utmost value. However, undertaking the strict protocols outlined by the OSCILLATE trial rather than the usual local HFOV or CV policy/protocol posed implications. Before starting the OSCILLATE trial pilot, the principal investigators questioned whether trial protocols would be similar to centres’ usual practices in the HFOV arm of the trial. A self-reporting survey was e-mailed to charge from hospital (3). Early randomized controlled trials (RCTs) investigating the use of high-frequency oscillatory ventilation (HFOV) in ARDS compared conventional mechanical ventilation (CV) with HFOV. Although these trials showed a potential reduction in mortality with HFOV, the strategies that were used in the CV protocols are not currently considered to be lung protective (4,5). In addition, small sample sizes were used in these trials (6,7), which may have impacted the generalizability of the results to a broader ARDS population, and introduced potential misrepresentation and bias. Recently, a larger RCT of HFOV versus CV for early ARDS was conducted, and results contrasted those of earlier trials showing that HFOV failed to improve mortality in ARDS (8). These results now cause critical care clinicians caring for ARDS patients to question what modality of mechanical ventilation to use during the late phase of ARDS.

The pilot phase of the trial was conducted from July 2007 to June 2008, and the main trial from July 2009 to August 2012. Five hundred forty-eight of the planned 1200 patients were randomly assigned to receive either HFOV following a lung-protective protocol of high set frequency coupled with a prescribed high maximum power and lung recruitment manoeuvres (8-11), or CV using a lung-protective strategy of low tidal volume, high positive end-expiratory pressure and lung-recruitment manoeuvres modelled after the experimental arm of the Lung Open Ventilation Study (12). On recommendation of the data monitoring committee, the trial was stopped early because interim analysis revealed no decrease in mortality with HFOV – and perhaps a tendency toward harm.

Because the OSCILLATE trial compared two mechanical ventilation strategies, involvement of and reliance on respiratory therapists (RTs) was of utmost value. However, undertaking the strict protocols outlined by the OSCILLATE trial rather than the usual local HFOV or CV policy/protocol posed implications. Before starting the OSCILLATE trial pilot, the principal investigators questioned whether trial protocols would be similar to centres’ usual practices in the HFOV arm of the trial. A self-reporting survey was e-mailed to charge RTs at multiple Canadian hospitals practicing HFOV before the pilot phase of the trial to observe what HFOV parameters were being used. Pretrial, both frequency and mean airway pressure tended to be set lower in many centres. These differences in practice may have made it more challenging for bedside RTs at participating centres because they would have to consciously refer to the OSCILLATE protocol rather than providing their usual HFOV care with ease, thereby increasing their workload. In fact, for centres experienced with HFOV for ARDS, some reported that the protocol varied with respect to parameters, such as mean airway pressure and power, causing them to be more conscious to avoid straying from the protocol. Centres with minimal previous HFOV experience reported an even greater imposition of work on the RTs.

In participating OSCILLATE trial centres, research coordinators (RCs) performed the tasks of daily collection of ventilatory data, arterial blood gases, cointerventions (sedation, neuromuscular blocking agents, steroids, vasopressor requirements, etc) and reporting any protocol violations. In some centres, the RC’s clinical background was in respiratory therapy; others included registered nurses or other backgrounds. However, in some of the centres, where either the RC was not an RT or there was not an RC employed, they relied heavily on the bedside clinical RTs to collect the required ventilator data and ventilator protocol violations, thus increasing their daily workload. Reporting of protocol violations alerted the trial coordinating centre to how well specific centres were adhering to the protocol. This allowed for timely feedback to be provided to the respective centres so that study results would be based on protocol rather than an alternative method.

Today, the trial continues to have implications for RTs. Based on trial results, RTs – in consultation with the critical care team – must now decide on how best to provide mechanical ventilatory support for adult ARDS patients using HFOV or CV. The OSCILLATE trial demonstrated that early institution of HFOV in adult patients with moderate to severe ARDS did not decrease mortality, but may have increased it. The challenge now for RTs is whether to use HFOV for adults with moderate to severe ARDS. If a decision has been made to use HFOV, at what stage of ARDS should it be initiated? The option to institute HFOV in later, moderate to severe ARDS should not be discounted because this subset of patients has not been separately studied, nor have alternative HFOV protocols using different parameter options, such as lower mean airway pressures, been studied. The question remains: what is the role (if any) of HFOV in ‘late’ ARDS? An RCT for this group of patients, perhaps with a redesigned protocol, would likely be welcomed by the critical care community.

There is currently an OSCILLATE trial knowledge translation initiative underway, funded by the Canadian Institutes of Health Research, involving centres that were involved with the OSCILLATE trial (25 centres in Canada and one in Saudi Arabia). Retrospective data are being collected on practice patterns in the management of adults with moderate to severe ARDS in 2014. Once summarized, these descriptive practice patterns for ARDS will help critical care staff compare their practice with others, as well as with ARDS management guidelines currently under development by the American Thoracic Society. Identified practice patterns will also help researchers identify other areas for knowledge translation, identification and frequency of use of mechanical ventilation strategies that are currently being used (but not well investigated) for ARDS. This includes airway pressure release ventilation and deciding on the most appropriate control group mechanical ventilator parameters for future RCTs in ARDS, inclusive of novel ventilatory strategies and pharmaceuticals.
REFERENCES

BIOGRAPHICAL NOTE
Lori Hand is a clinical research coordinator for international multicentre critical care trials with the Department of Clinical Epidemiology and Biostatistics at McMaster University, Hamilton, Ontario. Lori is also a site research coordinator at Hamilton General Hospital, and has participated in critical care trials in mechanical ventilation, sepsis, nutrition and thromboembolism prophylaxis. She is also a staff respiratory therapist and certified hyperbaric technician at Hamilton General Hospital.
Helping to treat your symptomatic patients is all in a day’s work…

ONBREZ® BREEZHALER®

Demonstrated fast, 5-minute onset (week 12; FEV₁ improvement shown 5 minutes after first dose 0.1 L; p<0.001, serial FEV₁ measurement; secondary endpoint)†

Maintained round-the-clock (24-hour) bronchodilation (LS mean FEV₁ (L) vs. placebo at week 12, p<0.001; secondary endpoint)
- time points were 5 min, 30 min, 1 hr, 2 hrs, 4 hrs, 6 hrs, 12 hrs, 16 hrs, 22 hrs, and 24 hrs1,2†

Improved transition dyspnea index (LS mean TDI focal score at week 12, 1.34 vs. 0.11 for placebo, p<0.001; secondary endpoint)1,3

Indication & clinical use:
ONBREZ® BREEZHALER® (indacaterol maleate) is a long-acting β₂-agonist (LABA) indicated for long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.
- Not indicated for the relief of acute deterioration of COPD, for asthma, or for use in patients under 18 years of age

Contraindications:
- Not indicated for treatment of asthma

Most serious warnings and precautions:
Asthma-related death: Increased risk of asthma-related death is considered a class effect with LABAs, including indacaterol maleate. ONBREZ® BREEZHALER® is not indicated for asthma.

Other relevant warnings and precautions:
- Not indicated for acute episodes of bronchospasm
- Increased risk of cardiovascular effects
- Caution in patients with cardiovascular disorders
- Caution in patients with convulsive disorders, thyrotoxicosis and patients who are unusually responsive to β₂-adrenergic agonists
- Risk of hypokalemia and hyperglycemia
- Paradoxical bronchospasm
- Immediate hypersensitivity
- Should not be used in patients with acutely deteriorating COPD
- Should not be used concomitantly with other LABAs
- May inhibit labour

FEV₁: forced expiratory volume in 1 second; LS: least square; TDI: transition dyspnea index.
† B2355: A 12-week, multicentre, randomized, double-blind, placebo-controlled, parallel-group study assessing the safety and efficacy of ONBREZ® BREEZHALER® 75 mcg once daily vs. placebo in patients with COPD (n=318).
‡ From a subset of 239 patients in B2355. FEV₁ data shown is ONBREZ® BREEZHALER® vs. placebo, respectively: 5 min: 1.56 vs. 1.39; 30 min: 1.57 vs. 1.38; 1 hr: 1.56 vs. 1.38;
  2 hrs: 1.56 vs. 1.37; 4 hrs: 1.53 vs. 1.30; 6 hrs: 1.48 vs. 1.30; 12 hrs: 1.43 vs. 1.39;
  16 hrs: 1.39 vs. 1.24; 22 hrs: 1.40 vs. 1.27; 24 hrs: 1.40 vs. 1.34.
§ B2354: A 12-week, multicentre, randomized, double-blind, placebo-controlled, parallel-group study assessing the safety and efficacy of ONBREZ® BREEZHALER® 75 mcg once daily vs. placebo in patients with COPD (n=323).
¶ Comparative clinical significance has not been established.

References: 1. ONBREZ® BREEZHALER®
Surfactant: The importance of documented policy and procedure

Ron Valotaire RRT

The current issue of the Canadian Journal of Respiratory Therapy includes an excellent—and timely—review by Nouraeyan et al (1) (pages 91-95) on surfactant administration in the neonatal population. Care of this fragile group has improved greatly since the early days of neonatology. Huge strides have been made on the obstetrical side, which makes our job in the neonatal intensive care unit (NICU) significantly easier than it once was. Advances in maternal screening for infection, drugs and congenital anomalies, among others, have led to earlier and improved treatment.

In the NICU, our grasp of the importance of nutritional needs in the low birth weight population has improved immensely over the past 10 to 15 years. The leaps in technology have enabled us to fine-tune conventional ventilation and synchronize very closely to the patients’ needs in all phases of the ventilatory cycle. The technology and expertise in high-frequency ventilation have also shown exponential growth. However, there is one area that has shown a remarkable lack of consistency in its application. Surfactant plays such a vital role in the reduction of mortality and morbidity, and yet, after 30 years of widespread use, many facilities do not have a documented policy and procedure, let alone one based on current evidence.

We are all aware that one of the main components of increased work of breathing is low functional residual capacity (FRC). Positive pressure ventilation (PPV), in the form of appropriate peak inspiratory pressure and positive end-expiratory pressure, is required to achieve effective FRC. However, one of the first things we are taught as respiratory therapists is that there is no safe level of PPV. If you are administering PPV, in whatever form that may take, you are causing damage to the lungs in varying degrees.

This is where surfactant enters the fray. When given early and effectively, surfactant can help establish FRC while allowing the practitioner to use lower pressures and, therefore, mitigate damage to the premature lung. The question once was: what is the best way to administer surfactant via the endotracheal tube? Well, as this article by the group from the Montreal Children’s Hospital (Montreal, Quebec) shows, the question has been answered. Bolus administration, ideally in one aliquot if tolerated, via a multi-access catheter to a patient in supine position with head mid-line, is the way to go. The article explains the rationale for this quite nicely, and most Level III units adhere to this practice. There are outliers, however, and that is why we need a standardized protocol that is easily accessible and teachable. In India, the pharmaceutical company that markets one type of surfactant will not allow practitioners to administer the surfactant until they have read and signed a comprehensive package based on the latest practices and literature available. The Montreal groups’ efforts are a significant step in that direction.

In Canada, the Evidence-based Practice for Improving Quality (EPIQ) group has talked about putting their heads together and developing a best practice standard. EPIQ is essentially a representative collection of health care providers from neonatal units across the country striving to raise quality and continuity of care to the highest level by shared practices and use of benchmarking in a highly collaborative manner. Hopefully the article by Nouraeyan et al (1) and the Montreal groups’ efforts will help kick start such an endeavour.

REFERENCE
CALENAD OF EVENTS

2014


2015

January 29-31, Toronto, Ontario: 2015 Better Breathing Conference. Contact the Ontario Lung Association, 18 Wynford Drive, Suite 401, Toronto, Ontario M3C 0K8. Telephone 888-344-LUNG (5864), e-mail info@on.lung.ca, website www.betterbreathing.ca


April 15-18, Geneva, Switzerland: 2015 European Lung Cancer Conference. Contact the European Society for Medical Oncology, Via L, Taddei 4, Lugano, Ticino 6962, Switzerland. Telephone 41-91-973-1900, fax 41-91-973-1902, e-mail esmo@esmo.org, website www.esmo.org

April 25-28, Vancouver, British Columbia: 2015 Canadian Conference on Medical Education. Contact Ms Chris Holloway, Conference Manager, 265 Carling Avenue, Suite 800, Ottawa, Ontario K1S 2E1. Telephone 613-730-0687 ext 240, fax 613-730-1196, e-mail cholloway@afmc.ca, website www.mededconference.ca

May 21-24, Calgary, Alberta: Canadian Society of Respiratory Therapists Educational Conference and Trade Show. Contact the Canadian Society of Respiratory Therapists, Katherine Nollet, 201-2460 Lancaster Road, Ottawa, Ontario K1B 4S5. Telephone 613-731-3164, fax 613-521-4314, website www.csrt.com

June 6-10, Seattle, Washington: SLEEP 2015, the 29th Annual Meeting of the Associated Professional Sleep Societies. Contact the American Academy of Sleep Medicine, 2510 North Frontage Road, Darien, Illinois 60561 USA. Telephone 630-737-9700, fax 630-737-9790, e-mail sleepmeeting@apss.org, website www.sleepmeeting.org

June 7-9, Winnipeg, Manitoba: 69th Annual Meeting of the Canadian Society of Otolaryngology (CSO). Contact the CSO, Donna Humphrey, General Manager, 221 Millford Crescent, Elora, Ontario N0B 1S0. Telephone 519-846-0630, fax 519-846-9529, e-mail cso@sympatico.ca, website www.ecfs.eu
ULTIBRO® BREEZHALER® (indacaterol maleate and glycopyrronium bromide) is a combination of a long-acting β2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA), indicated for the long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.1

Consult the Product Monograph at www.novartis.ca/UltibroMonograph for contraindications, warnings, precautions, adverse reactions, interactions, dosing, and conditions of clinical use. The Product Monograph is also available by calling 1.800.363.8883.


ULTIBRO and BREEZHALER are registered trademarks. Product Monograph available on request.

© Novartis Pharmaceuticals Canada Inc. 2014
Respiratory Resource is the educational platform of the Canadian Society of Respiratory Therapists. It is a place where members can share guidelines, policies, medical directives, case studies, and presentations.

There is ongoing education in the form of Webinars, Journal Clubs and Directed Reading Articles.

**JOURNAL CLUB**

Journal Club is a great way to keep up-to-date with current research. Journal Club consists of a group of CSRT members reviewing a research article together (online). All members who sign up will be asked to pre-read the article so the online chat and discussion will be done in a timely manner. CSRT members who participate will receive 2 CE credits.
Can J Respir Ther Vol 50 No 3 Autumn 2014 81

AnchorFast Guard
Oral Endotracheal Tube Fastener

Provide an extra measure of protection—
with confidence.

The new AnchorFast Guard oral endotracheal tube fastener features an integrated tube protection sleeve to help prevent tube occlusion.

See how we’re helping you put patients first—
with confidence. Call 1.800.263.7400 or visit
www.anchorfast1.com

Now with tube protection

Hollister

Smoking and tobacco use is the single largest preventable cause of lung disease and death in Canada.

The Canadian Lung Association encourages people who smoke to get support and learn how to quit.

To find local quit support, contact your local Lung Association.

Grifols is a global healthcare company whose mission is to improve the health and well being of people around the world. Grifols produces high quality plasma medicines for patients with life-threatening diseases. Our plasma medicines treat patients in the following therapeutic areas: Bleeding disorders, Immune deficiencies, Pulmonary (lung) disease, Life-threatening infections, Shock and blood loss, Neurological disorders (CIDP).

THE LUNG ASSOCIATION
L’ASSOCIATION PULMONAIRE

GRIFOLS pioneering spirit

www.lung.ca
We are looking for new and experienced peer reviewers with expertise in the following areas (and more):

- Aerosols
- ARDS
- Asthma
- Anesthesia
- Cardiac Care
- Critical Care
- Clinical Trials
- COPD
- Ventilation
- Oxygen Therapy
- CPAP
- Emergency Medicine
- ECMO
- Evidence Based Practice
- Neonatology
- Obstructive Sleep Apnea
- Oscillation
- Population Health
- Quality improvement
- Resuscitation
- Sepsis
- Sleep Medicine
- Spirometry
- VAP
- Education
- Leadership

The Canadian Journal of Respiratory Therapy (CJRT) is a quarterly, peer reviewed publication. Our goal is to generate evidence and discussion to support more effective and equitable access to respiratory therapy and care for patients in Canada and around the world.

Peer reviewers are required to evaluate the suitability of research manuscripts for publication and ensure that the research/literature review is adequately portrayed. As a reviewer for the CJRT, you will be expected to:

- Commit the appropriate amount of time required for review (reviewers are generally given 14 days to review a paper)
- Review manuscripts using our online system, PulsusTrack
- Disclose any conflicts of interest, financial or otherwise, related to a particular manuscript

REVIEWER RECOGNITION

The CJRT is proud to recognize the efforts of our reviewers by publishing a list of our reviewers on the CJRT website, and sending thank-you letters from the Editor-in-Chief at the end of each year (a letter is also available to be mailed to your employer recognizing your contributions).

HOW TO APPLY

If you want to participate in the dissemination of knowledge through a professional journal, please send a letter outlining your interest to:

editor@csrt.com
Prediction of endotracheal intubation outcome in opioid-poisoned patients: A clinical approach to bispectral monitoring

Nastaran Eizadi-Mood MD, Ahmad Yaraghi MD, Mahsa Alikhasi MD, Mitra Jabalameli MD, Shadi Farsaei PharmD, Ali Mohammad Sabzghabaee PharmD

BACKGROUND: Some opioid-poisoned patients do not respond appropriately to naloxone; consequently, intubation is required. Although various measures have been used to evaluate the level of consciousness of poisoned patients, no study has assessed the role of the bispectral index (BIS) to ascertain the depth of anesthesia in opioid-poisoned patients who require endotracheal intubation.

OBJECTIVE: To compare BIS scores between opioid-poisoned patients with and without intubation, and to determine the BIS cut-off point for endotracheal intubation in these patients.

METHODS: In the present cross-sectional study, conducted in an Iranian university referral hospital for poisoning emergencies between 2012 and 2013, opioid-poisoned patients (n=41) were divided into two groups according to their requirement for endotracheal intubation. BIS analyses were performed at the time of admission and at the time of intubation for those who required it. In addition, electromyography and signal quality index were evaluated for all patients at the time of admission, and cardiorespiratory monitoring was performed during the hospitalization period. Using ROC curves, and sensitivity and specificity analyses, the optimal BIS cut-off point for prediction of intubation of these patients was determined.

RESULTS: The optimal cut-off point for prediction of intubation was BIS ≤78, which had a sensitivity of 86.7% (95% CI 66.1 to 98.8) and specificity of 88.5% (95% CI 73.9% to 98.8%); the positive and negative predictive values were 81.2% and 92%, respectively.

CONCLUSIONS: BIS may be considered an acceptable index to determine the need for intubation in opioid-poisoned patients whose response to naloxone is inadequate.

Key Words: Bispectral index (BIS); Endotracheal intubation; Naloxone; Opioid poisoning

The high prevalence of mortality among individuals who engage in opiate injection drug use remains an ongoing problem in many countries, and needs an effective drug policy and public health action (1). A flood of opioids has resulted in a rising tide of deaths in recent decades (2). In fact, deaths from opiate overdose exceed the number of homicide deaths in New York City (New York, USA), which is estimated to be 900 each year (3). Clinical patterns of opioid intoxication and of opioid antagonist failure to produce an adequate response, especially with evidence of respiratory depression (6).

Various indexes have been evaluated to determine the need for intubation in critically ill patients (6-8). Not only is a Glasgow Coma Scale (GCS) score ≤8 a useful guide for endotracheal intubation in patients with brain injury resulting from respiratory compromise, it also indicates the need for intubation in cases for which the cause of unconsciousness is poisoning (9,10).

Another index used to measure the level of consciousness and depth of anesthesia and sedation is the bispectral index (BIS) (11). In 1996, the United States Food and Drug Administration approved a novel measure of the level of consciousness by algorithmic processing of a patients' electroencephalographic data for assessing the hypnotic effects of general anesthetics and sedatives (12,13). BIS monitoring was initially used primarily during operative anesthesia. Recently, however, BIS monitoring has become a reasonable approach used in intensive care unit (ICU) patients to assess the depth of sedation, especially among individuals receiving neuromuscular paralysis.
Despite the potential application of the BIS for monitoring the depth of anesthesia, to our knowledge, its role has yet to be evaluated for patients who were unable to protect their airway despite naloxone administration (6).

The outcomes were followed based on BIS measured at admission and before intubation of the included patients. The BIS ranges from 0 (equivalent to electroencephalogram silence) to 100, which indicates complete alertness (17).

In addition, electromyography and signal quality index were evaluated for all patients at the time of admission; cardiac and respiratory monitoring were also performed during the hospitalization period.

All data were analyzed using SPSS version 16 (IBM Corporation USA) and Med-Calc (Med-Calc Software Inc, Belgium) statistical software.

The χ² or Fisher’s exact test was applied to compare categorical data between patients with and without endotracheal intubation; P<0.05 was considered to be statistically significant. In addition, significant differences in continuous data were determined using the Mann-Whitney U test or an independent-samples t test where appropriate. ROC curves were used for discrimination by comparison of areas under the curve (AUC) (22). Acceptable and excellent discrimination were defined as AUC 0.7 to 0.8, and 0.8 to 0.9, respectively (23). Therefore, according to the result of ROC curve analyses, sensitivity, specificity and the optimal cut-off point were determined (24). This BIS cut-off point was used to determine predicted and observed endotracheal intubation in poisoned patients.

RESULTS

Endotracheal intubation was required in 15 of the 41 opioid-poisoned patients evaluated in the present study. No patient died during the study and, among patients who completed the study, 10 (66.7%) in the intubation group and 21 (80.8%) in the nonintubation group experienced improvement without complications (P=0.45). In contrast, five patients in each group showed improvement but experienced complications (33.3% versus 19.2%; P=0.45).

Demographic data and clinical findings of patients, including route and cause of poisoning, type and amount of ingested opioid, use of concomitant medication, time to first treatment modality and length of hospitalization, were compared between intubated and nonintubated patients (Table 1). Fisher’s exact test and χ² tests showed significant differences in employment status, use of concomitant medication, time to first treatment modality and length of hospitalization; P<0.05 was considered to be statistically significant. In addition, significant differences in continuous data were determined using the Mann-Whitney U test or an independent-samples t test where appropriate. ROC curves were used for discrimination by comparison of areas under the curve (AUC) (22). Acceptable and excellent discrimination were defined as AUC 0.7 to 0.8, and 0.8 to 0.9, respectively (23). Therefore, according to the result of ROC curve analyses, sensitivity, specificity and the optimal cut-off point were determined (24). This BIS cut-off point was used to determine predicted and observed endotracheal intubation in poisoned patients.

METHODS

The present cross-sectional study was conducted at the Noor and Ali Asghar [PUH] University hospital affiliated with Isfahan University of Medical Sciences (Isfahan, Iran) between 2012 and 2013. This centre, the major referral medical centre for toxicological emergencies in central Iran, is facilitated, staffed and designed for the management of poisoning patients, of whom approximately 400 are admitted monthly.

Patients included in the present study were all opioid-poisoning individuals who were admitted to the ward during the study period. Patients hospitalized for opioid poisoning were randomly selected using a random number table and their identification number. The study protocol was approved by the Institutional Board of Human Studies at Isfahan University of Medical Sciences. In addition, after the study was accurately explained to the patients, informed consent for inclusion was obtained. Discharge and/or death before study commencement were considered to be exclusion criteria.

Forty-one patients hospitalized for opioid poisoning were recruited for the present study and were followed to measure outcomes. Initially, adequate supportive primary care was performed for all opioid-poisoned patients and treatment to facilitate the recovery process was continued. Demographic data and clinical findings from the patients, including vital signs, hemodynamic parameters, routine blood biochemistry analysis, clinical history at admission, amount of ingested opioids, performed treatment modality (eg, gastric lavage, activated charcoal) and length of hospitalization, were recorded for further analysis. If intubation was necessary to control airway and oxygenation, time of intubation was also documented. This information was collected from patient charts and documented reports of emergency services. Expedient endotracheal intubation was performed for patients who were unable to protect their airway despite naloxone administration (6).

The BIS ranges from 0 (equivalent to electroencephalogram silence) to 100, which indicates complete alertness (17). Several studies have shown a positive correlation between BIS values and GCS and Acute Physiology And Chronic Health Evaluation (APACHE II) scores (11,18,19). A previous review article (8) discussed the different methodologies used to monitor the depth of anesthesia and described potential applications of the BIS for such a purpose.

(14-16). The BIS ranges from 0 (equivalent to electroencephalogram silence) to 100. A manufacturer-recommended value between 40 and 60 is suitable for general anesthesia (17).

All data were analyzed using SPSS version 16 (IBM Corporation USA) and Med-Calc (Med-Calc Software Inc, Belgium) statistical software.

TABLE1
Demographic data and clinical characteristics of the study patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intubated (n=15)</th>
<th>Nonintubated (n=26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean ± SD</td>
<td>41.93±3.21</td>
<td>33.69±2.40</td>
<td>0.046</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>10 (66.7)</td>
<td>22 (84.6)</td>
<td>0.25*</td>
</tr>
<tr>
<td>Female</td>
<td>5 (33.3)</td>
<td>4 (15.4)</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>5 (33.3)</td>
<td>10 (38.5)</td>
<td>0.74†</td>
</tr>
<tr>
<td>Married</td>
<td>10 (66.7)</td>
<td>16 (61.5)</td>
<td></td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>7 (46.7)</td>
<td>21 (80.8)</td>
<td>0.038†</td>
</tr>
<tr>
<td>Unemployed</td>
<td>8 (53.3)</td>
<td>5 (19.2)</td>
<td></td>
</tr>
<tr>
<td>Route of poisoning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>13 (86.7)</td>
<td>24 (92.3)</td>
<td>0.62*</td>
</tr>
<tr>
<td>Nonoral</td>
<td>2 (13.3)</td>
<td>2 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Cause of poisoning</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unintentional (accidental)</td>
<td>6 (40)</td>
<td>18 (69.2)</td>
<td>0.07†</td>
</tr>
<tr>
<td>Intentional</td>
<td>9 (60)</td>
<td>8 (30.8)</td>
<td></td>
</tr>
<tr>
<td>Type of opioid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methadone</td>
<td>12 (80)</td>
<td>21 (80.8)</td>
<td>0.09*</td>
</tr>
<tr>
<td>Heroin</td>
<td>3 (20)</td>
<td>1 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Other opioids</td>
<td>–</td>
<td>4 (15.4)</td>
<td></td>
</tr>
<tr>
<td>Using concomitant medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11 (73.3)</td>
<td>8 (30.8)</td>
<td>0.008*</td>
</tr>
<tr>
<td>No</td>
<td>4 (26.7)</td>
<td>18 (69.2)</td>
<td></td>
</tr>
<tr>
<td>Time to first treatment modality, h, mean ± SD</td>
<td>6.38±1.65</td>
<td>2.52±0.65</td>
<td>0.025</td>
</tr>
<tr>
<td>Length of hospitalization, h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤48</td>
<td>6 (40)</td>
<td>26 (100)</td>
<td>0.001*</td>
</tr>
<tr>
<td>&gt;48</td>
<td>9 (69)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Data presented as n (%) unless otherwise indicated. *Fisher’s exact test; †χ² test
treatment modality among intubated compared with nonintubated patients. Moreover, Mann-Whitney U test analysis was used to compare the mean values of blood biochemistry parameters during the first two days of admission between the two groups (Table 2). This analysis showed significant differences in some factors of arterial blood gases including HCO₃⁻ base excess and PaO₂ (P=0.03, 0.02 and 0.02, respectively). Finally, mean values of hemodynamic indexes, electromyography and BIS were compared between groups using t tests at admission and at intubation (Table 3). The related results demonstrated that mean systolic blood pressure (SBP), electromyography results, signal quality index and BIS were significantly lower among intubated compared with nonintubated patients.

A ROC analysis of data to evaluate the best point of BIS for prediction of intubation was performed. According to this analysis, BIS ≤78 was the best point for intubation prediction, with 86.7% sensitivity (95% CI 66.1% to 98.8%) and 88.5% specificity (95% CI 73.9% to 98.8%), with associated positive and negative predictive values of 81.2% and 92%, respectively.

**DISCUSSION**

Endotracheal intubation may prevent respiratory failure and aspiration in opioid-poisoned patients who fail to respond to naloxone and meet the criteria for intubation (25). The primary purpose of the present study was to determine the optimal BIS cut-off point to predict the need for endotracheal intubation in opioid-poisoned patients. Among the 41 patients (age range 24 to 50 years) recruited during the study period, 36.6% underwent intubation. According to the results of the present study, patient age was a significant factor for intubation. Previous studies have reported that vital signs and hemodynamic parameters are dependent on patient age, and that older patients may experience more acute signs of poisoning (26). Although the reason for poisoning did not significantly affect patient intubation status in the present study, intubated patients had a more prevalent history of opioid exposure (95% CI 66.1% to 98.8%) and 88.5% specificity (95% CI 73.9% to 98.8%), with associated positive and negative predictive values of 81.2% and 92%, respectively.

The value of the BIS for the intubation of opioid-poisoned patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intubated (n=15)</th>
<th>Nonintubated (n=26)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN, mmol/L</td>
<td>7.27±0.96</td>
<td>14.21±7.21</td>
<td>0.08</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>116.69±9.72</td>
<td>111.38±10.61</td>
<td>0.63</td>
</tr>
<tr>
<td>Serum Na*, mMol/L</td>
<td>129.86±0.76</td>
<td>137.50±1.17</td>
<td>0.21</td>
</tr>
<tr>
<td>Serum K*, mMol/L</td>
<td>4.37±0.24</td>
<td>5.05±0.30</td>
<td>0.09</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>25.72±5.40</td>
<td>41.75±10.88</td>
<td>0.03</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>22.8±2.95</td>
<td>95.00±36.22</td>
<td>0.01</td>
</tr>
<tr>
<td>PT, s</td>
<td>17.45±1.80</td>
<td>24.62±8.88</td>
<td>0.14</td>
</tr>
<tr>
<td>PTT, s</td>
<td>40.2±8.89</td>
<td>50.00±17.51</td>
<td>0.59</td>
</tr>
<tr>
<td>Glucose, mMol/L</td>
<td>7.04±1.17</td>
<td>5.26±0.28</td>
<td>0.31</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>43.31±1.26</td>
<td>41.71±1.88</td>
<td>0.61</td>
</tr>
<tr>
<td>Platelets, x10⁹/L</td>
<td>232.24±31.18</td>
<td>213.67±29.46</td>
<td>0.64</td>
</tr>
<tr>
<td>INR</td>
<td>3.10±0.70</td>
<td>2.76±0.31</td>
<td>0.86</td>
</tr>
<tr>
<td>HCO₃⁻, mMol/L</td>
<td>21.25±0.88</td>
<td>26.63±1.48</td>
<td>0.03</td>
</tr>
<tr>
<td>BE, mMol/L</td>
<td>-12.4±0.60</td>
<td>-9.12±0.88</td>
<td>0.02</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>77.28±6.05</td>
<td>90.00±5.70</td>
<td>0.17</td>
</tr>
<tr>
<td>PaCO₂, mmHg</td>
<td>48.07±3.39</td>
<td>51.21±4.49</td>
<td>0.39</td>
</tr>
<tr>
<td>pH</td>
<td>7.24±0.51</td>
<td>7.32±0.02</td>
<td>0.11</td>
</tr>
<tr>
<td>PaO₂, mmHg</td>
<td>55.33±5.84</td>
<td>39.04±4.45</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD unless otherwise indicated. *Mann-Whitney U test. ALT Alanine aminotransferase; AST Aspartate aminotransferase; BE Base excess; BUN Blood urea nitrogen; INR International normalized ratio; PaO₂ Partial pressure of arterial oxygen; PaCO₂ Partial pressure of carbon dioxide; PT Prothrombin time; PTT Partial thromboplastin time; SaO₂ Oxygen saturation

**TABLE 2**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intubated (n=15)</th>
<th>Nonintubated (n=26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At admission</td>
<td>97.18±8.50</td>
<td>113.00±3.33</td>
<td>0.001</td>
</tr>
<tr>
<td>At intubation</td>
<td>97.18±28.22</td>
<td>113.33±5.77</td>
<td>0.36</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At admission</td>
<td>67.71±3.41</td>
<td>63.13±6.66</td>
<td>0.21</td>
</tr>
<tr>
<td>At intubation</td>
<td>67.71±9.03</td>
<td>63.31±11.55</td>
<td>0.53</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At admission</td>
<td>36.82±0.88</td>
<td>36.07±0.92</td>
<td>0.51</td>
</tr>
<tr>
<td>At intubation</td>
<td>37.08±0.17</td>
<td>37.01±0.10</td>
<td>0.96</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At admission</td>
<td>77.73±6.42</td>
<td>84.0±2.47</td>
<td>0.31</td>
</tr>
<tr>
<td>At intubation</td>
<td>73.18±10.78</td>
<td>77.00±5.48</td>
<td>0.86</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At admission</td>
<td>11.72±1.47</td>
<td>22.92±4.75</td>
<td>0.03</td>
</tr>
<tr>
<td>At intubation</td>
<td>14.28±3.93</td>
<td>16.0±2.00</td>
<td>0.83</td>
</tr>
</tbody>
</table>

EMGA, %

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intubated (n=15)</th>
<th>Nonintubated (n=26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>At admission</td>
<td>41.28±9.29</td>
<td>74.68±6.46</td>
<td>0.01</td>
</tr>
<tr>
<td>At intubation</td>
<td>51.40±15.72</td>
<td>47.50±47.50</td>
<td>0.93</td>
</tr>
</tbody>
</table>

BIS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intubated (n=15)</th>
<th>Nonintubated (n=26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>At admission</td>
<td>67.26±2.67</td>
<td>85.50±1.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>At intubation</td>
<td>71.61±1.92</td>
<td>83.00±10.44</td>
<td>0.08</td>
</tr>
</tbody>
</table>

SOI

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Intubated (n=15)</th>
<th>Nonintubated (n=26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>At admission</td>
<td>100.00±2.00</td>
<td>100.00±2.00</td>
<td>1</td>
</tr>
<tr>
<td>At intubation</td>
<td>100.00±2.00</td>
<td>100.00±2.00</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD unless otherwise indicated. *Parameters measured at two time points: on admission and at the time of intubation for patients who required endotracheal intubation; ‘At intubation’ parameters in nonintubated patients were measured at the same time as those for intubated patients.
BIS analysis showed that BIS was significantly lower in intubated patients at both admission to the ICU and at intubation. The present study showed that BIS ≤78, with specificity of 88.5% and sensitivity of 86.7%, was an appropriate criterion to predict the need for intubation in opioid-poisoned patients. Another study reported that correlation between GCS and BIS analysis is highest when BIS <80 and GCS score <8 are used as cut-off points (19).

**CONCLUSION**

Because coadministration of other sedatives with opioids occurred in some poisoned patients, they did not respond adequately to naloxone and, consequently, intubation was required. Our study showed that BIS may be an acceptable index to determine the need for intubation in these patients.

**ACKNOWLEDGEMENTS:** This study was part of a Doctor of Medicine thesis project and was financially supported by the Vice-chancellor for research and technology at Isfahan University of Medical Sciences (IUMS, Research Project Number 291002). The authors acknowledge the staff in Isfahan Clinical Toxicology Research Center and the department of clinical toxicology at IUMS for their help and support.
To PAPR or not to PAPR?

Vanessa Roberts BSc RRT

The present outbreak of Ebola has health care professionals seeking guidance on isolation precautions for routine care and aerosol-generating procedures (AGPs). The most recent guidelines state that during AGPs, health care professionals should wear respiratory protection at least as protective as a National Institute for Occupational Safety and Health-certified fit tested N95 filtering face piece respirator or higher; for example, a powered air-purifying respirator (PAPR). The present review discusses the advantages and disadvantages of using a PAPR versus an N95 mask, and relates the experience of the Jewish General Hospital (Montreal, Quebec) of PAPR policy implementation. Training programs on proper donning and doffing of personal protective equipment and quality control systems need to be in place. Respiratory therapists are frontline during AGPs and need to be active in the decision making of the type of equipment chosen to protect them.

Key Words: Aerosol-generating procedures; Ebola; Infection control; Personal protective equipment; Powered air-purifying respirator

Infection prevention and control precautions are implemented for contact droplet/airborne transmissions, as well as routine precautions. These precautions include the appropriate use of personal protective equipment (PPE) as indicated by hospital policy. The present outbreak of Ebola viral disease (EVD) has health care personnel seeking guidance on the appropriate use of PPE for suspected cases that may arrive to their facility. The 2007 Centers for Disease Control and Prevention (CDC, Georgia, USA) Guideline for Isolation Precautions (1) emphasize that the route of transmission dictates recommendation for infection control measures; however, the question remains as to what PPE is required for aerosol-generating procedures (AGPs). Do we use powered air-purifying respirators (PAPRs) or N95 masks? Are there advantages or disadvantages to using a PAPR, and is there a recommended procedure for donning and doffing?

EBOLA ROUTE OF TRANSMISSION

Taking the Ebola outbreak as an example, we need to understand how it is transmitted. Ebola hemorrhagic fever is caused by infection with the Ebola virus, a member of the family Filoviridae, a severe and often fatal illness in humans. The mode of transmission to humans is through close contact with the blood, secretions, or organs of ill or deceased chimpanzees, gorillas or fruit bats. Human-to-human transmission occurs by direct contact (through broken skin and mucous membrane) with infected blood, body fluids, secretions or organs of an infected person (2,3). To date, airborne transmission has not been documented; therefore, early recognition of an individual with suspected EVD is critical for infection control (3).

Clinical symptoms of EVD include sudden onset of fever >38°C, malaise, myalgia, headache, conjunctival injection (red eye), pharyngitis, vomiting, diarrhea that can be bloody, gastrointestinal pain, and impaired kidney and liver function (4-6). The incubation period varies from two to 21 days, with seven days being the average. Currently, experimental treatments have been tested in animals, but have been provided/administered on a compassionate basis to humans without knowledge of effect or safety (3).

Respiratory protection in health care for contact droplet/airborne precautions commonly follows two filtering device paths, N95 mask respirators and PAPRs. Currently, the CDC and the WHO have no clear guidelines on AGPs and the use of N95 versus PAPRs. The N95 mask filter at least 95% of particles <5 μm in diameter and are not resistant to oil. These masks have the advantages of blocking aerosol (<5 μm) and droplet-size (5 μm to 50 μm) particles, are readily available, allow the use of stethoscopes, are noiseless and do not require a power source (Figure 1). Their disadvantages include requiring an initial and periodic fit testing, the possibility of being compromised by an improper fit (eg, because of facial hair), poor tolerance by users due to breathing resistance, and heat and moisture build up, the high cost of stocking different types and sizes, and the potential for contamination due to exposed face and neck (7,8).

A PAPR is a battery-powered blower that provides positive airflow through a filter, cartridge, or canister to a hood or face piece. The type and amount of airborne contaminant will dictate the type of filter, cartridge or canister required for the PAPR. The National Institute for Occupational Safety and Health (NIOSH) tests different respirator models in its laboratory to ensure they meet certain minimum performance standards and it is the employer's responsibility to assess the respiratory precaution needs and ensure that the correct filter, cartridge or canister is purchased (9). Cartridges/filters are colour coded; for example, P100 filters are coded purple.

Utiliser l’ARAA ou non?

La présente écllosion du virus Ebola incite les professionnels de la santé à chercher des conseils sur les précautions en matière d’isolement dans les soins habituels et les interventions produisant des aérosols (IPA). D’après les lignes directrices les plus récentes, pendant les IPA, les professionnels de la santé devraient porter un dispositif de protection des voies respiratoires qui leur procurera une barrière au moins aussi efficace qu’un masque N95 ayant fait l’objet d’un essai d’ajustement certifié par le National Institute for Occupational Safety and Health, tel qu’un appareil respiratoire à adduction d’air (ARAA). La présente analyse traite des avantages et des inconvénients de l’ARAA par rapport au masque N95 et rend compte de l’expérience de l’Hôpital général juif de Montréal, au Québec, qui a adopté une politique d’utilisation de l’ARAA. Il faut adopter des programmes de formation sur la mise en place et le retrait convenables du dispositif de protection personnelle ainsi qu’un système de contrôle de la qualité. Les inhalothérapeutes sont en première ligne pendant les IPA et doivent participer à la prise de décision sur le type de matériel retenu pour les protéger.

Respirators: N95 or PAPR?

Exposure to the Ebola virus in the health care setting occurs when infection control precautions are not strictly practiced by health care workers (ie, not wearing appropriate PPE). The CDC has released infection prevention and control recommendations for hospitalized patients with known or suspected Ebola hemorrhagic fever in the United States (4). Table 1 summarizes of the main CDC recommendations for hospitalized patients with known or suspected EVD, and includes the standard contact and droplet precautions.

RESPIRATORS: N95 OR PAPR?

©2014 Canadian Society of Respiratory Therapists. All rights reserved
### TABLE 1
Summary of the main Centers for Disease Control and Prevention (Georgia, USA) recommendations for hospitalized patients with known or suspected Ebola virus disease

<table>
<thead>
<tr>
<th>Component</th>
<th>Recommendation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient placement</td>
<td>Single patient room (containing a private bathroom) with the door closed. Facilities should maintain a log of all persons entering the patient’s room</td>
<td>Consider posting personnel at the patient’s door to ensure appropriate and consistent use of PPE by all persons entering the patient room.</td>
</tr>
</tbody>
</table>
| **PPE**          | All persons entering the patient room should wear at least:  
 |                  | - Gloves  
 |                  | - Gown (fluid resistant or impermeable)  
 |                  | - Eye protection (goggles or face shield)  
 |                  | - Facemask  
 | Additional PPE may be required in certain situations (eg, copious amounts of blood, other body fluids, vomit or feces present in the environment), including but not limited to:  
 |                  | - Double gloving  
 |                  | - Disposable shoe covers  
 |                  | - Leg coverings | Recommended PPE should be worn by HCP on entry into patient rooms or care areas. On exit from the patient room or care area, PPE should be carefully removed without contaminating one’s eyes, mucous membranes or clothing with potentially infectious materials and either  
 |                  | - Discarded, or  
 |                  | - For reusable PPE, cleaned and disinfected according to the manufacturer’s reprocessing instructions and hospital policies. | Instructions for donning and removing PPE have been published. |
| **AGPs**         | Avoid AGPs for Ebola hemorrhagic fever patients  
 |                  | If performing AGPs, use a combination of measures to reduce exposures from AGPs when performed on Ebola hemorrhagic fever patients  
 |                  | Visitors should not be present during AGPs  
 |                  | Limiting the number of HCPs present during the procedure to only those essential for patient care and support  
 |                  | Conduct the procedures in a private room and ideally in an Airborne Infection Isolation Room (AIIR) that is a negative pressure room, when feasible. Room doors should be kept closed during the procedure except when entering or leaving the room, and entry and exit should be minimized during and shortly after the procedure  
 |                  | HCPs should wear gloves, a gown, disposable shoe covers, and either a face shield that fully covers the front and sides of the face or goggles, and respiratory protection that is at least as protective as a NIOSH-certified fit-tested N95 filtering face piece respirator or higher (eg, powered air-purifying respirator or elastomeric respirator) during AGPs  
 |                  | Conduct environmental surface cleaning following procedures  
 |                  | If re-usable equipment or PPE (eg, powered air-purifying respirator, elastomeric respirator, etc) are used, they should be cleaned and disinfected according to manufacturer instructions and hospital policies  
 |                  | Collection and handling of soiled reusable respirators must be performed by trained individuals using PPE as described above for routine patient care | Although there are limited data available to definitively define a list of AGPs, procedures that are usually included are bilevel positive airway pressure, bronchoscopy, sputum induction, intubation and extubation, and open suctioning of Airways. |
| **Hand hygiene** | HCPs should perform hand hygiene frequently, including before and after all patient contact, contact with potentially infectious material, and before donning and doffing PPE, including gloves  
 |                  | Health care facilities should ensure that supplies for performing hand hygiene are available | Hand hygiene in health care settings can be performed by washing with soap and water, or using alcohol-based hand rubs. If hands are visibly soiled, use soap and water, not alcohol-based hand rubs |

Data adapted from reference 4. AGPs Aerosol-generating procedures; HCP Health care practitioner; NIOSH National Institute for Occupational Safety and Health; PPE Personal protective equipment

---

**Figure 1** Examples of National Institute for Occupational Safety and Health-certified N95 masks, courtesy of 3M (USA) (11) and Moldex (USA) (12)

High-efficiency particulate air (HEPA) filters have a similar filtration as P100 (ie, they filter at least 99.97% of particles 0.3 μm in diameter and are oil proof) (9) and are the filters of choice for infection control airborne precautions. The use of HEPA filters in PAPRs implies that they have a greater level of respiratory protection than N95 masks. They also have the advantage of providing head and neck protection, do not require fit testing because of a full hood, are approved for use with facial hair and allow for continuous bedside care of a patient. Their disadvantages include difficulties in communicating due to their bulk and noise, the inability to use a stethoscope and a requirement for electricity (batteries) to ensure proper airflow rates into the hood. After use, filters are considered to be contaminated with infectious material; therefore, they pose a potential risk to individuals reprocessing reusable respirators (9).
The most commonly used models of PAPRs available for respiratory protection are manufactured by 3M (USA) and Bullard (USA) (10); however, a list of NIOSH-approved respirators can be obtained online at www.cdc.gov/niosh/npptl/respusers.html. The 3M Air-Mate HEPA is the model purchased by the Jewish General Hospital in Montreal, Quebec. It consists of a mounted battery-operated respirator with disposable black tubing and a double-shrouded hood (Figure 2). The rechargeable battery must be tested routinely by a designated individual. Before using the PAPR, one must ensure that the HEPA filter and gasket are in place. The black tube connects to the PAPR and the blower is tested by placing a nipple in the tube and ensuring that it rises according to manufacturer’s specifications (Figure 3). The tube is then attached to the hood and the blower turned on before placing the hood over the face (Figure 4).

The correct sequence of donning, doffing and hand hygiene is important to the effectiveness of the PAPR and the N95 mask. The greater protection provided by a PAPR over a N95 mask for droplet and airborne particles is reduced if one self-contaminates with a disease that is transmitted via contact; hence, the importance of proper training. When donning, the shoe cover (which may or may not be used) is first and then the gown (ensuring it is tied at the back). The N95 mask or the PAPR is secured after verifying the flow, and the face shield or the loose-fitting hood is placed over the face, with the inner shroud tucked inside the gown. Then hand hygiene, and the long-cuffed gloves go over the sleeves of the gown.

The removal of PPE should be performed at least 2 m away from the patient, near the door. The shoe cover, gloves and gown should be removed inside the room, and a trained assistant should be available to help you remove and clean the PAPR. The hood or face shield and N95 mask should only be removed outside the patient’s room, and then placed in a biohazard bag. All PPE should be removed so as not to self-contaminate. Hand hygiene should be performed after glove removal – before removal of the face mask and after removal of all PPE (7,8). The advantage of using the N95 mask for AGPs is that it is disposable and does not place additional personal at risk; hence, the CDC’s statement for EVD “Because of the potential risk to individuals reprocessing reusable respirators, disposable filtering face piece respirators are preferred” (4).

In cases in which a health care worker cannot be fit-tested for an N95 mask or has facial hair, the use of a PAPR is an alternative. Also, in situations in which a live airborne virus is being handled, a PAPR may be preferred to the N95 mask.

EXPERIENCE AT THE JEWISH GENERAL HOSPITAL
The Ebola outbreak has reminded our team that we have PAPRs in our institution (purchased in anticipation of the H1N1 epidemic), and that we do not have a policy for when it is required and how it is used. Only two members of hospital staff were trained on donning, doffing and cleaning of the PAPR. We are now developing a policy on the use of PAPRs, which will be followed by training sessions for staff identified as potentially requiring their use. During H1N1, we used the waterproof gown, long-cuff nitrile glove, N95 mask and face shield for all AGPs with success. As respiratory therapists, we still use N95 masks as a routine precaution during bronchoscopies and intubations because there have been situations in which samples returned positive for airborne infection and the patient was not under airborne precautions.

Hospital infection control policy makers have been left to decide whether a PAPR should be used for EVD. What is clear is that we must be proactive because it is just a question of time before an infected patient arrives in Canada. As part of a disaster infection control plan, there must be provisions for training in the use of all types of PPE for health care workers who may be involved in the care of an infected or suspected case, and there must be proper quality control systems in place. The decision to use a PAPR for AGPs without a program in place can lead to more self-contaminations than using appropriate PPE with a fit-tested N95 mask.

Additional information regarding EVD, including risk assessment, diagnosis and treatment, can be accessed at: www.cdc.gov/vhf/ebola/hcp/infection-prevention-and-control-recommendations.html. The Public Health Agency of Canada also has information for health care professional at: www.phac-aspc.gc.ca/id-mi/vhf-fvh/ebola-eng.php.
CONCLUSION
The use of PAPRs (although effective in the PPE armamentarium, similar to the other respirators) has its advantages and disadvantages. Its use has not yet found a specific niche, EVD being no exception. The Infection Prevention and Control Department of the Jewish General Hospital recently developed a policy for infection control precautions for EVD and ensured that it was reviewed by a multidisciplinary team including the respiratory therapy department. It is extremely important as respiratory therapists that we ensure that our role in AGPs is identified and our needs are met. All respiratory therapy departments should be proactive and ensure that their hospitals have policies in place.

REFERENCES
Surfactant administration in neonates: A review of delivery methods

Nina Nouraeyan MD1, Alicia Lambrinakos-Raymond MD1, Marisa Leone RRT2, Guilherme Sant’Anna MD PhD FRCPC3

Surfactant has revolutionized the treatment of respiratory distress syndrome and some other respiratory conditions that affect the fragile neonatal lung. Despite its widespread use, the optimal method of surfactant administration in preterm infants has yet to be clearly determined. The present article reviews several aspects of administration techniques that can influence surfactant delivery into the pulmonary airways: the bolus volume, injection rate, gravity and orientation, ventilation strategies, alveolar recruitment, and viscosity and surface tension of the fluid instilled. Based on the present review, knowledge gaps regarding the best way to administer surfactant to neonates remain. From the available evidence, however, the most effective way to optimize surfactant delivery and obtain a more homogeneous distribution of the drug is by using rapid bolus instillation in combination with appropriate alveolar recruitment techniques.

Key Words: Neonatology; Preterm infant; Respiratory distress syndrome; Review; Surfactant administration; Ventilation

Treatment with exogenous surfactant has saved the lives of thousands of premature babies in the past few decades (1). The therapeutic efficiency of a given surfactant preparation correlates with its lipid and protein composition (and other factors), but it is also highly dependent on the technique used for administration. It is important to use a delivery strategy that optimizes surfactant distribution into the pulmonary airways to maximize its beneficial effects (2). In 2014, the Committee on Fetus and Newborn – American Academy of Pediatrics published a clinical report on the use of surfactant replacement therapy for respiratory distress in the preterm and term neonate (1). Among several recommendations, the report stated that “the optimal method of surfactant administration in preterm infants has yet to be clearly proven”. Unfortunately, the scientific literature provides conflicting and limited data regarding the methods or techniques of surfactant administration. The majority of studies were performed long ago and tested in more mature infants (gestational age >28 weeks), which does not reflect the population of preterm infants that actually undergo endotracheal intubation and surfactant treatment. Moreover, respiratory care has changed substantially since these studies were conducted.

Exogenous surfactant preparations must spread rapidly and efficiently into the air-liquid interface once instilled in the proximal airways, with the goal of achieving a homogeneous distribution throughout the lungs. However, rapid administration of liquid into the lungs may elicit transient oxygen desaturation and bradycardia, or significant complications such as severe airflow obstruction, pulmonary hemorrhage, pneumothoraces or pulmonary hypertension (3). Therefore, surfactant should be administered according to a well-established protocol under the supervision of clinicians and respiratory therapists experienced in tracheal intubation, ventilator management and general care of the premature infant.

The present article reviews several aspects of administration techniques that can influence the delivery of surfactant into the lungs: the bolus volume, injection rate, gravity and orientation, ventilation strategies and development of airway obstruction, alveolar recruitment, and viscosity and surface tension of the fluid instilled. A surfactant administration protocol that was developed and implemented in our unit, based on the best available evidence, is included in Appendix 1.

BOLUS ADMINISTRATION AND INJECTION RATE

There are two common modes of delivering surfactant into the pulmonary airways: bolus infusion (one or multiple aliquots); or continuous infusion (2) (Box 1). Surfactant has also been given by nebulization; however, because this method and preparation remain under investigation, it will not be reviewed here.

In general, slower techniques of surfactant bolus administration have been noted to be inferior to the rapid bolus technique (4). When rapid bolus infusions were compared with slow bolus or continuous

©2014 Canadian Society of Respiratory Therapists. All rights reserved
infusions in several animal studies, they were noted to be superior in terms of overall distribution of the surfactant and a faster rate of improvement of oxygenation and lung compliance (5,6). However, side effects, such as transient bradycardia and decreased blood pressure, were noted with rapid bolus administration. At present, the rapid bolus technique remains the recommended method of surfactant administration.

Cassidy et al (7) showed that the method of liquid instillation affects how the liquid distributes within the lung. The best method allowed the formation of a liquid plug in the trachea at the beginning of surfactant instillation. The liquid was then driven to the distal parts of the lung by ventilation, resulting in quicker spread in a few breaths and more uniform liquid distribution throughout the lungs. Transit and delivery times depend on plug volume, among other factors. Although the exogenous surfactant takes in the order of minutes to reach the alveoli, the lowering of surface tension at the distal ends occurs very rapidly—within seconds—as the result of the compression of the endogenous surfactant (8).

GRAVITY AND ORIENTATION

When surfactant is administered slowly (slow infusion and/or slow rate of ventilation), the distribution is dependent on the orientation of the airways with respect to gravity (4,5,9). This could lead to overinflation of the parts of the lung receiving surfactant and result in bronchopulmonary dysplasia (6). Improved homogeneity is achieved in the supine compared with upright positioning. Animal models have also shown greater epithelial cell injury at slower propagating speeds (10). In a randomized control trial (11), there was no difference in clinical outcomes when two fractional doses of surfactant were given in two body positions, compared with four fractional doses given in four positions.

VENTILATION STRATEGIES AND DEVELOPMENT OF AIRWAY OBSTRUCTION

Surfactant has been administered either by disconnecting the infant from the ventilator and applying bagging, or by continuing ventilation during the procedure. Using beractant at a volume of 4 mL/kg, Zola et al (11) conducted a multicentre, randomized control trial comparing three different strategies of surfactant instillation: two doses, removing patient from the ventilator; two doses, continuing ventilation during the procedure; and four doses, removing patient from the ventilator. Ventilation during all three procedures was performed by using pre-treatment pressures: fraction of inspired oxygen (FiO\textsubscript{2}) = 1.0; respiratory rate at least 60 breaths/min; and an inspiratory time of 0.5 s. There were no significant differences among the three procedures. A similar study was conducted by Valls-i-Soler et al (12), who compared two methods. The first was bolus delivery (two aliquots) of poractant alfa at a volume of 2.5 mL/kg, with the patient removed from the ventilator and hand-bagged for 1 min with the same FiO\textsubscript{2} used before the procedure and adjusting the peak inflation pressure (PIP) for adequate chest expansion. The second method was delivery via a side hole, in which a full dose of surfactant was rapidly given in 60 s via a 3.5 Fr catheter introduced through a side hole. Mechanical ventilation was not interrupted, but PIP was increased by 10% for 5 min. Both methods were noted with rapid bolus administration. At present, the rapid bolus technique remains the recommended method of surfactant administration.

A prospective study was performed in smaller and more immature preterm infants receiving their first or second dose of surfactant while being ventilated in assist control volume guarantee mode (13). A small volume of poractant alfa (1.25 mL/kg) was given as a single bolus using a closed technique during ventilation (ventilation not interrupted during administration). Ventilator parameters were recorded before, during and after administration. A complete cessation (ie, obstruction) of flow down the endotracheal tube (ETT) was observed in 21 of 22 (95%) of infants. Following surfactant administration, PIP increased from a mean of 19 cmH\textsubscript{2}O (range 16 cmH\textsubscript{2}O to 22 cmH\textsubscript{2}O) up to 27 cmH\textsubscript{2}O (range 23 cmH\textsubscript{2}O to 30 cmH\textsubscript{2}O), taking 30 min to 60 min to return to baseline. A significant and prolonged decrease in the delivered tidal volume (obstruction) was noted in the majority of the infants. Airway obstruction immediately after surfactant administration was also noted by Miedema et al (14) in 15 preterm infants receiving surfactant while on high-frequency oscillatory ventilation, despite a lung recruitment manoeuvre used before surfactant administration. Tarawneh et al (3) prospectively evaluated a standardized protocol for a bovine lipid extract surfactant administration using a dose of 5 mL/kg. According to the protocol, surfactant was given in four aliquots using a closed technique without removing the patient from the ventilator. A significant number of extreme low birth weight infants experienced episodes of severe airway obstruction, requiring removal of the ETT followed by reintubation.

Anderson et al (15) investigated the effects of breathing frequency on liquid distribution. At 60 breaths/min, the liquid is first deposited on the airway walls and then transmitted toward the gravity-dependent region of the lung over the ensuing breaths. A more uniform distribution of liquid throughout the lung was obtained. This phase lasted only a few minutes and facilitated the transport of liquid to its target location. After this initial targeted instillation is achieved, normal ventilation using appropriate ventilation rate can be used. The implication for surfactant delivery is that a slow rate of ventilation could result in nonhomogeneous surfactant distribution. This is not the desired outcome because it may inflate parts of the lung receiving surfactant, resulting in lung injury.

ALVEOLAR RECRUITMENT

Recruitment of the lungs before surfactant treatment can minimize ventilation-induced lung injury and facilitate the distribution of surfactant into the pulmonary airways. In newborn piglets, a volume recruitment manoeuvre using moderately increased tidal volume applied before, during and for an additional 5 min after surfactant administration led to a superior clinical response in terms of gas exchange and lung function, owing to a more homogeneous distribution pattern (16). Surfactant distribution was also evaluated in a study in which a recruitment manoeuvre to determine the optimal peak end-expiratory pressure (PEEP) level was performed in newborn piglets before surfactant administration. In one-half of the animals, an additional recruitment manoeuvre was performed to define a new PEEP level after surfactant administration. Using electrical impedance tomography, an improved spatial distribution of regional lung ventilation was observed in animals that underwent a postsurfactant recruitment manoeuvre. This recruitment manoeuvre was then applied in 15 preterm infants receiving surfactant while on high-frequency oscillatory ventilation. A rapid increase (5 min) followed by stabilization of lung volume was observed, with the most prominent effect in the dependent (dorsal) lung regions, supporting the role of gravity in surfactant distribution.

VISCOSITY AND SURFACE TENSION OF THE FLUID INSTILLED

Commercial surfactants also differ in surface viscosity. Viscosity is believed to influence the rate, extent and uniformity of distribution of surfactant in the lungs. Preparations with lower surface viscosity are preferred for endotracheal application because it allows a more uniform and rapid distribution of the instilled surfactant with less loss due to coating of the upper airways. The viscosity of surfactant preparations is directly dependent on phospholipid concentration and inversely related to temperature. After 15 min at a temperature of 37°C, viscosity increases exponentially. In fact, after 30 min at this temperature, the viscosity of calf surfactant and beractant were 20 times higher when compared with values measured at 10 min (17). In an animal experiment, Lewis et al (18) compared beractant and a bovine lipid extract surfactant. A significantly improved distribution was achieved with the bovine lipid extract surfactant, which was demonstrated to have a viscosity eight times lower than beractant.
A more viscous liquid yields a more homogeneous distribution, and a less viscous plug penetrates more deeply into the distal airways. There are several surfactant preparations available for use in neonates. A natural bovine lipid extract surfactant is used in the majority of Canadian neonatal units. The biochemical composition of each preparation generally reflects the composition of natural surfactant obtained from the alveolar spaces, at least with respect to the high content of phospholipids and the high proportion of disaturated dipalmitoyl phosphatidylcholine (DPPC). The production procedure should also, in principle, preserve the hydrophobic proteins SP-B and SP-C. Surfactants produced from bronchoalveolar lavage are, in principle, less contaminated with plasmatic and tissue components: bovactant, calfactant, bovine lipid extract surfactant, and a biological product produced from pig lungs in Cuba. Poractan alfa and beractant are examples of surfactant obtained from minced lungs. The resulting proportion of the main surface-active lipid component, DPPC, varies from 70% in beractant, 40% in calfactant, approximately 35% to 56% in poractan alfa, 41% in the bovine lipid extract surfactant and 45% in the biological product produced from pig lungs in Cuba.

OTHER FACTORS
Experimental studies have demonstrated that the level of endogenous surfactant can have important consequences in surfactant replacement therapy. Pre-existing surfactant can slow the spreading of new surfactant by diminishing the differential in tension between surfactant-rich and surfactant-poor poor areas (19). In addition, the new surfactant can induce a disturbance through the existing surfactant. Once a patient is treated with the first dose of surfactant, it could be more difficult for subsequent doses to reach the periphery, hindering the overall delivery and efficacy of the product. This could be the reason of the observed decrease in benefits of the administration of three or more doses compared with one or two doses (20).

CONCLUSION
The present review discussed some of the mechanisms that influence the instillation of surfactants into the pulmonary airways. In light of the evidence from animal and human studies, we believe that the optimal method for surfactant delivery should include the use of bolus instillation combined with ventilatory strategies before (lung recruitment), during (disconnection and bagging or increase on ventilator settings to provide sufficient pressure and a rate of 60 breaths/min) and after surfactant administration (lung recruitment). Extra care should be taken when giving surfactant to extremely low birth weight infants because this is a population at higher risk for side effects such as severe episodes of airway obstruction during the procedure (3). As for any protocol, each neonatal intensive care unit should develop a coherent administration strategy with the goal of achieving targeted delivery of surfactant that enhances safety and efficacy of this medication.

APPENDIX: PROTOCOL FOR SURFACTANT REPLACEMENT ADMINISTRATION AT MCGILL UNIVERSITY HEALTH CENTRE, MONTREAL, QUEBEC
Patient population:
- Patients with respiratory distress syndrome
- Patients with conditions associated with surfactant deficiency such as meconium aspiration syndrome, sepsis and pulmonary hemorrhage as per discussion with the most responsible physician. Although congenital diaphragmatic hernia is associated with surfactant deficiency, the administration of surfactant may result in significant deterioration and, therefore, should be used with caution.

CRITERIA FOR SURFACTANT ADMINISTRATION
a. <24 weeks’ gestational age: these infants should be intubated immediately after birth and surfactant given prophylactically (within the first 15 min to 30 min of life). Between intubation and surfactant administration, these infants should be ventilated very carefully with low tidal volume and pressures.

b. ≥24 weeks’ gestational age: h.1 For infants intubated immediately after birth, it is recommended that surfactant be given as early treatment (<2 h of age), except if the infant is on room air and minimal ventilatory support on neonatal intensive care unit admission. These infants should be immediately extubated to nasal ventilation or nasal continuous positive airway pressure.

b.2 Infants initially treated with noninvasive ventilation, endotracheal intubation and surfactant administration is recommended under one the following circumstances:
- Fraction of inspired oxygen (FiO₂) >0.5 (21-23) to maintain oxygen saturation (SpO₂) >88% or a partial pressure of arterial oxygen (PaO₂) >45 mmHg
- Partial pressure of arterial carbon dioxide (PaCO₂) >55 mmHg to 60 mmHg with a pH <7.25
- Apnea requiring bag and mask ventilation
- >6 apneas/6 h
- Evidence of significant work of breathing (retractions, grunting and chest wall distortion in infants presenting with increases in oxygen needs)

PROCEDURE
Physician will assess patient eligibility for surfactant administration and write an order for surfactant to be given. Physician should be at bedside during surfactant administration. The registered respiratory therapist (RRT) will advise the bedside nurse that the patient will be receiving surfactant. The RRT and registered nurse will perform a baseline patient assessment, which should include:
1. Respiratory assessment: respiratory rate, ventilator pressures, tidal volumes and transcutaneous PCO₂ (TcPCO₂)
2. Chest assessment: air entry, adventitious sounds, symmetry of chest expansion, secretions
3. Vital signs: heart rate, oxygen saturation (SpO₂), blood pressure
4. Patient status: awake, asleep, sedated
5. Chest x-ray review to assess endotracheal tube (ETT) position and lung volume

EQUIPMENT SET-UP
The RRT should set up the equipment as follows:
- a) Retrieve surfactant from the freezer and warm to room temperature for no more than 30 min before its use. The vial can be rolled but DO NOT shake it.
- b) Calculate the amount of surfactant needed.
- c) Swab the vial rubber cap with an alcohol swab before introducing needle. Fill syringe with surfactant.
- d) Attached luer lock syringe with medication to luer fitting.
- e) Attach trach care mac cartridge to Y.
- f) Before attaching trach care mac to patient, prime the interval volume of the catheter with medication.
- g) Attach trach care mac adaptor to ventilator circuit and ETT.

INTERVENTION BEFORE SURFACTANT DELIVERY
The RRT perform the following interventions:
1. Pre-oxygenation: the oxygen concentration should be increased to achieve SpO₂ >95% before surfactant delivery.
2. Suction ETT and listen to the air entry.
3. Lung recruitment manoeuvre: Provide five to 10 inflations with pressures 1 cmH₂O to 2 cmH₂O above previous ventilatory settings to assure some lung recruitment before administration, which would facilitate drug distribution into the pulmonary airways.
4. Record all vital signs (heart rate, blood pressure, SpO₂ and TcPCO₂).
The acute treatment response to surfactant results from the biophysical properties of surfactant AND depends on the rapid distribution of surfactant to the lungs.

The magnitude of the distribution problem is generally not appreciated. There are approximately 20 generations (branch points) from the trachea to the respiratory bronchioles and sacculles. Therefore, there are approximately 250,000 binary branch points and 500,000 distal airways leading to sacculles in the preterm lung. If the distribution is not proportionate to the number of sacculles distal to each branch point, then surfactant distribution will not be uniform. Any nonuniformity at a proximal branch point will be amplified at subsequent branch points.

When surfactant is instilled into a lung, the distribution results from the following principles:

<table>
<thead>
<tr>
<th>Property</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surface activity</td>
<td>Causes rapid adsorption and spreading</td>
</tr>
<tr>
<td>Gravity</td>
<td>Surfactant distributed by gravity in large airways</td>
</tr>
<tr>
<td>Volume</td>
<td>Higher volumes, cause better distributions</td>
</tr>
<tr>
<td>Rate of administration</td>
<td>Rapid administration improves distribution</td>
</tr>
<tr>
<td>Ventilator settings</td>
<td>Pressure and PEEP help clear airways of fluid</td>
</tr>
<tr>
<td>Fluid volume in the lungs</td>
<td>Higher volumes of fetal lung fluid or edema fluid improves distribution</td>
</tr>
</tbody>
</table>

PEEP: Positive end-expiratory pressure

Therefore, treatment techniques do matter. Surfactant will distribute to the preterm lung more uniformly when given rapidly and at higher volumes (see Table above).

The slow infusion of surfactant into the lungs to minimize any acute physiological changes during treatment can result in very poor distribution. Using a slow rate of administration could result in a nonhomogeneous surfactant distribution, which is not the desired outcome.

Administration of surfactant to extreme preterm infants using multiple aliquots and with the patient receiving mechanical ventilation at the same settings before delivery of the drug was associated with severe episodes of airway obstruction. (3)

The practical ways to improve distribution are to position the infant to minimize gravity, to give surfactant quickly in a reasonable volume and to give the infant enough ventilatory support to quickly clear the airways of fluid.

The effect of surfactant to open the lungs results in a rapid increase in oxygenation that can occur almost instantaneously. The subsequent responses to surfactant treatment result from improved lung mechanics, which may change more gradually and will depend, in part, on the choice of ventilator styles.

SURFACANT ADMINISTRATION

The RRT should administered surfactant as follows:

1. Surfactant should be delivered through an in-line catheter with the tip located at the mid trachea level.
2. Because the surfactant actually available at the Units is the bovine lipid extract surfactant and the dose should be 5 mL/kg (135 mg phospholipids/kg) divided into one or a maximum of two aliquots.
3. Mode of delivery: surfactant should be given as bolus infusion (10 s to 20 s).
4. Infant should be disconnected from the ventilator and bagged by a physician or another RRT with the flow inflating bag or T-piece device at a rate of 60 inflations/min and pressure necessary to push the surfactant effectively into the pulmonary airways.

PEEP: Positive end-expiratory pressure

5. Start the bagging approximately 5 s after initiation of surfactant administration (to give some time for the formation of a fluid plug or column of surfactant into the ET). The flow rate of the flow inflating bag should be the minimum necessary to provide adequate pressures.
6. Infant should be kept in the horizontal position during the entire procedure.
7. When using more than one aliquot, a minimum period of 30 s to 60 s between the aliquots should be used if infants remained stable.
8. Vital signs and ventilator parameters should be monitored during the delivery process.
9. Details regarding surfactant administration given should be written in the medical records (time, number of aliquots, PIP and PEEP used, vital signs and complications).
10. The ETT should not be suctioned for following 2 h unless signs of significant airway obstruction occur.

POSTSURFACANT ADMINISTRATION

1. Registered nurse should record vital signs immediately after administration is completed and every 10 min for the next hour.
2. RRT should record ventilator parameters every 15 min for the next hour.

REFERENCES


Generous Supporters of the
Canadian Journal of Respiratory Therapy
Website

ADVERTISERS’ INDEX

The Canadian Journal of Respiratory Therapy is a peer-reviewed journal, financed almost entirely through advertising. The companies advertising in the Journal recognize the need to support high-quality, Canadian, ethical journals and to promote publishing of Canadian medical research.

The support of the following companies is appreciated:

Almirall Ltd
Tudorza Genuair .......................... IFC, IBC
BOMImed/Hamilton Medical
Compact ICU Ventilators. .................... 67
Boehringer Ingelheim (Canada) Ltd
Respirat ........................................ 68
Cardinal Health Canada
WILAmed AIRcon Respiratory Humidifier ....... 73
Grifols Canada Ltd
Corporate ....................................... 81

Hollister Limited
AnchorFast Guard ................................ 81
Maquet-Dynamed Inc
Servo Ventilator Platforms. .................... 70
Novartis Pharmaceuticals Canada Inc
Onbreez Breezhaler ......................... 76/77
Ultibro Breezhaler ............................. 79
Seebri Breezhaler .............................. 75/OBC

3M Canada
SpotOn Temperature Monitoring System .......... 78
INTRODUCING TUDORZA® GENUAIR®
A new LAMA in COPD*

Imagine the possibilities

TUDORZA GENUAIR demonstrated a statistically significant improvement in lung function (morning pre-dose [trough] FEV1) at 24 weeks vs. placebo (TUDORZA GENUAIR 400 mcg BID, 55 mL vs. placebo, -73 mL, p<0.0001)²,³†

Indications and clinical use:
TUDORZA GENUAIR (aclidinium bromide) is indicated as a long-term maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

• TUDORZA GENUAIR is not indicated for the relief of an acute deterioration of COPD
• Indicated in patients >18 years of age

Other relevant warnings and precautions:
• Should not be used for the initial treatment of acute episodes of bronchospasm (i.e., as rescue therapy)
• Should not be initiated in patients with acutely deteriorating COPD
• Should not be used more often or at higher doses than recommended
• Should not be used more frequently than twice daily
• Patients who have been taking inhaled, short-acting bronchodilators on a regular basis should start using them only for symptomatic relief; patients not on a short-acting bronchodilator should be provided one for symptomatic relief of acute symptoms
• Worsening of narrow-angle glaucoma
• Worsening of urinary retention
• Immediate hypersensitivity reactions; patients with a history of hypersensitivity reactions to atropine should be closely monitored
• Paradoxical bronchospasm
• Use with caution in patients with certain cardiovascular conditions
• Occurrence of headache or blurred vision may influence the ability to drive or use machinery

For more information:
Please consult the Product Monograph at http://webprod5.hc-sc.gc.ca/dpd-bdpp/index-eng.jsp for important information relating to adverse reactions, drug interactions, and dosing information, which have not been discussed in this piece.

The Product Monograph is also available on request by calling 1-800-957-7679. For the complete Formulary listing, please visit the Ontario Drug Benefit website at: http://www.health.gov.on.ca/en/public/programs/drugs/programs/odb/odb.aspx

* LAMA: Long-Acting Muscarinic Antagonist; COPD: Chronic Obstructive Pulmonary Disease.
† A randomized, double-blind, placebo-controlled, 24-week study in patients aged ≥40 years (N=819) with a clinical diagnosis of stable moderate-to-severe COPD (post-bronchodilator FEV1 of ≤30% to <80% of predicted normal value) and a history of smoking of at least 10 pack-years. Morning trough (pre-dose) FEV1 was defined as FEV1 measured 12 hours after the previous evening dose of TUDORZA GENUAIR.


TUDORZA® and GENUAIR® are registered trademarks of Almirall SA. Almirall Limited and Forest Laboratories Canada Inc. are authorized to co-promote the product under the registered trademarks in Canada. © 2014 Almirall SA. All Rights Reserved.
PART OF THE NOVARTIS COPD PORTFOLIO

Open up to a LAMA option in COPD

IMPROVED PATIENTS’ QUALITY OF LIFE

(LS mean change in SGRQ total score vs. placebo, -3.32; *p<0.001)†

ONCE-DAILY PrSEEBRI® BREEZHALER®
DEMONSTRATED 5-MINUTE ONSET AND 24-HOUR BRONCHODILATION

FEV₁, improvement shown 5 minutes after first dose (0.093 L vs. placebo, *p<0.001, serial spirometry)‡

Significantly greater LS mean FEV₁ vs. placebo demonstrated at all time points over 24 hours (LS mean FEV₁ [L] vs. placebo after first dose, *p<0.001; time points were 5 min, 15 min, 30 min, 1 hr, 2 hrs, 3 hrs, 4 hrs, 6 hrs, 8 hrs, 10 hrs, 12 hrs, 23 hrs 15 min, 23 hrs 45 min)§

Indication & clinical use:
SEEBRI® BREEZHALER® is indicated as a long-term once-daily maintenance bronchodilator treatment in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

Not indicated for the relief of an acute deterioration of COPD

Can be used at the recommended dose in elderly patients 65 years of age and older

Should not be used in patients under 18 years of age

Relevant warnings and precautions:
Not indicated for treatment of acute episodes of bronchospasm

Not indicated for treatment of acutely deteriorating COPD

Worsening of narrow-angle glaucoma

Worsening of urinary retention

In severe renal impairment, use only if the expected benefit outweighs the potential risk

Paradoxical bronchospasm

Indication is based on an 18-week, randomized, double-blind, placebo-controlled parallel-group study assessing the efficacy and safety of SEEBRI® BREEZHALER® (glycopyrronium 50 mcg o.d.) in patients with COPD (n=525).

FEV₁ improvement shown 5 minutes after first dose (0.093 L vs. placebo, *p<0.001, serial spirometry)‡

Significantly greater LS mean FEV₁ vs. placebo demonstrated at all time points over 24 hours (LS mean FEV₁ [L] vs. placebo after first dose, *p<0.001; time points were 5 min, 15 min, 30 min, 1 hr, 2 hrs, 3 hrs, 4 hrs, 6 hrs, 8 hrs, 10 hrs, 12 hrs, 23 hrs 15 min, 23 hrs 45 min)§

For more information:
Please consult the Product Monograph at www.novartis.ca/asknovartispharma/download.htm?res=seebri%20breezhaler_scrip e.pdf&resTitleId=665 for important information relating to adverse events, drug interactions, and dosing information which have not been discussed in this piece. The Product Monograph is also available by calling the Medical Information Department at 1-800-363-8883.

LAMA: long-acting muscarinic antagonist; COPD: chronic obstructive pulmonary disease; LS: least square; SGRQ: St. George’s Respiratory Questionnaire, measures health-related quality of life in symptoms, activities and impact on daily life 5; FEV₁: forced expiratory volume in 1 second.

† GLOW2: A 52-week, randomized, double-blind, placebo-controlled parallel-group study of 1,060 patients with COPD. Patients received either SEEBRI® BREEZHALER® (glycopyrronium 50 mcg o.d.; n=525), placebo (n=268), or open-label tiotropium (18 mcg o.d.; n=267) as an active control. Primary endpoint was 24-hour post-dose (trough) FEV₁ following 12 weeks of treatment.

‡ GLOW1: A 26-week, randomized, double-blind, placebo-controlled parallel-group study to assess the efficacy, safety and tolerability of once-daily SEEBRI® BREEZHALER® (50 mcg) in patients with COPD (n=550), placebo (n=267).

§ LS mean FEV₁ (L) after first dose: SEEBRI® BREEZHALER® (n=169) vs. placebo (n=83), respectively: 5 min: 1.39 vs. 1.30; 15 min: 1.43 vs. 1.30; 30 min: 1.44 vs. 1.30; 1 hr: 1.47 vs. 1.30; 2 hrs: 1.52 vs. 1.30; 3 hrs: 1.53 vs. 1.30; 4 hrs: 1.54 vs. 1.30; 6 hrs: 1.48 vs. 1.33; 8 hrs: 1.47 vs. 1.31; 10 hrs: 1.47 vs. 1.32; 12 hrs: 1.45 vs. 1.31; 23 hrs 15 min: 1.37 vs. 1.27; 23 hrs 45 min: 1.30 vs. 1.31; p<0.001 for all time points.

References: