(Acta Anaesth. Belg., 2020, 71, 105-106)

A dedication to neuroanesthesia, research, and mentorship

V. Bonhomme (*,**,***), C. Franssen (*), M. Lamy (****)

Key words : Anesthesia ; resuscitation ; professionalism ; education ; intensive care medicine.

Last September 14, 2020, Professor Pol Hans (Figure) passed away after a long disease. We, the authors of this letter, had the privilege of professionally running alongside him for several years, and want here to underline his tremendous contribution to the anesthesia and intensive care specialty, in Belgium and outside Belgium. Professor Hans was not only an excellent clinician, always attentive to the needs and safety of patients, an excellent scientist, but also a rare teacher for youngers, and a real mentor for a lot of us. In this short synopsis, we would like to retrace his career, his accomplishments, and depict the extraordinary colleague and friend he was. This is the least we can do to honor his memory. We will honestly do this with our own perception of the character, and might therefore miss some elements of his personality. We apologize in advance for any undesirable omission.

Pol Hans was born in 1949. He graduated as a Medical Doctor at the University of Liege in 1975, and was immediately selected by Professor Marcel Hanquet to start a residency in anesthesiology and resuscitation. He obtained his specialist degree in 1979, and rapidly became one of the most faithful and brilliant collaborator of the Department of Anesthesia and Intensive Care Medicine of the Liege University Hospital, first exerting his clinical activity in the 'Baviere' Hospital, thereafter moving to the 'Citadelle' Regional Hospital until his retirement in 2011. He also practiced anesthesiology at the 'André Renard' Clinic, where he was the Head of the Anesthesia and Intensive Care Medicine Department. From the beginning, his main clinical focus of interest was the perioperative and anesthetic management of neurosurgical patients. He was among the pioneers in this domain, and he contributed a lot to its development in Belgium and abroad. His reputation was based on prolific clinical and basic research, which led to a PhD in 1983 and a total of more than 180 papers in national and international peer-reviewed journals, as well as 19 book chapters. His reputation was also sustained by his involvement in scientific societies such as the European Society of Anesthesiology, the 'Association de Neuroanesthésie-Réanimation de Langue Française', and the Society for Neuroscience in Anesthesia and Critical Care, and on innumerable invited conferences all over the

Professor Pol Hans

Vincent Bonhomme, MD, PhD ; Colette Franssen, MD, PhD ; Maurice Lamy, MD
(*) Department of Anesthesia and Intensive Care Medicine, University Hospital of Liege, Liege, Belgium
(**) University Department of Anesthesia and Intensive Care Medicine, CHR Citadelle, Liege, Belgium
(***) Anesthesia and Intensive Care Laboratory, GIGA-Consciousness Thematic Unit, GIGA-Research, Liege University, Liege, Belgium
(****) Honorary Professor of Anesthesia and Intensive Care Medicine and Retired Head of the Department of Anesthesia and Intensive Care Medicine, University Hospital of Liege and Liege University, Liege, Belgium
Corresponding author : Vincent Bonhomme, University Department of Anesthesia and Intensive Care Medicine, Bd du 12eme de Ligne, 1, 4000 Liege, Belgium.
Email : vincent.bonhomme@chuliege.be

world. Many consider him as a master of clinical research. As a clinician, he demonstrated a lot of rigor, exigence, and skillfulness, while not being any tyrant for those around him. Aside from his clinical and scientific activities, he was strongly involved in the teaching of anesthesiology and received the title of Clinical Professor from the Medicine Faculty of the University of Liege in 1997.

A characteristic of Pol Hans, on which everyone agrees, was his continuous commitment to teach anesthesia and resuscitation to trainees in anesthesiology, and his devotion to bring younger colleagues' career up by showing them how to undertake research and guiding them through the assault course of a PhD thesis. Many residents were often disputing the opportunity to spend a year with him, to beneficiate from his patience, kindness, knowledge, experience, and enthusiasm. He used to strengthen his teaching messages by unforgettable sentences such as : 'A good anesthesiologist is an aware individual beside a sleeping patient, and not the inverse', to underline the need for continuous vigilance of the anesthesiologist towards his/her patient welfare and safety. He was aiming at learning to residents not only to DO anesthesia, but more importantly to BE anesthesiologists in the best sense of the word, namely worried of patients entrusted to him/her. When a trainee had problems, he used to take him/her under his wing, and find a solution to overcome excessive stress, knowledge deficits, lack of confidence, social relationship difficulties, or personal problems. Mentorship was natural for him, through a healthy collaboration with colleagues, sharing of ideas, passionate discussions on several topics, and thoughtful guidance. He used to say that good research begins with asking oneself the good question, as simple as possible, and then think how it could be answered by designing the adequate experiment. He was an expert in reviewing texts and dissertations, kneading sentences until finding the perfect formulation. One of the most gratifying professional accomplishment for him was the acceptance of a good paper in a highly cited journal, whatever his place in the authors' list. We feel that every single anesthesiologist should have the chance to cross the road of such an exceptional mentor during the course of his/her career.

With a deadpan sense of humor, Pol Hans was maintaining a pleasant ambiance around him. He had strong rigor in work and a propensity to hardly afford hazardous organization, but stress never rubbed off around him. In line with his and his wife Danielle hospitableness, he had a liking for good wines, and was appreciating to share them with friends and colleagues. With Danielle, he was also strongly involved in social and humanitarian good deeds, such as the 'Médecins sans vacances' and 'Famille sans frontières' organizations. Not running after undeserved titles and honors was another trait of his personality.

With the departure of Pol Hans, the Belgian anesthesiology community has lost a figure, and we have to pay him a glowing tribute. He will remain an example for many of us.

(Acta Anaesth. Belg., 2020, 71, 107-110)

Feasibility of novel smartphone app-based pulse oximetry system compared with proprietary level 4 home sleep testing device for obstructive sleep apnea detection

E. Seet (*), C. Saw Jiayu (*), K.M. Leong (*), C.M. Kumar (*)

Keywords : Obstructive sleep apnoea ; mobile phone application ; airway ; sleep study.

Obstructive sleep apnea (OSA) is a chronic condition of sleep disordered breathing, characterized by upper airway obstruction, and intermittent episodes of apnea and hypopnea during sleep. It affects approximately 17% of men and 9% of women between 50-70 years old. Currently, there are substantial numbers of elective surgical patients with unrecognized OSA (1). Unrecognized severe OSA and longer cumulative time during sleep with oxygen saturation (SpO_2) < 80% has been recently reported to predict an increased risk of postoperative myocardial injury, stroke and cardiac death in surgical patients (1).

Pre-operative sleep monitoring devices have traditionally been categorized into 4 Levels based on the type of monitoring and physiological parameters measured (2). Polysomnography (PSG) is a Level I sleep study which includes a minimum of seven parameters (electroencephalogram, airflow, respiratory effort and oxygen saturation) and requires trained personnel in constant attendance. Unlike Level I, patients are unattended for Level II to IV studies. Level II devices measure both respiratory and sleep variables, while Level III and IV devices measure cardiorespiratory variables only, and do not assess sleep stages. Level III sleep studies measure a minimum of four cardiorespiratory variables, which include ventilation, oxygen saturation and heart rate or electrocardiography. On the other hand, level IV sleep devices are continuous recordings of a minimum of one parameter, which allows it to be the simplest form of portable sleep monitoring available.

Currently, PSG remains the gold standard for diagnosis of OSA. However, this requires extensive usage of manpower and hospital resources. Costs to the patient would generally be more than 1,000 US dollars. Level III and IV home sleep apnea devices can capture data for the diagnosis of OSA and are potential alternatives to PSG for diagnosing OSA in patients at high clinical risk of moderate to severe OSA (3), and have been shown to be sensitive and specific to detect OSA in surgical patients (4). However, data from these devices needs to be downloaded using proprietary software (e.g. Profox Associates, Inc, www.profox.net) and the process of calculating sleep disorder parameters can be inflexible and cumbersome.

In modern times mobile smartphones are readily available and phone-based applications are versatile at low costs. Smartphones have been rapidly adopted and are becoming the technological lynchpin of our current healthcare revolution. They facilitate database management and allow real time data processing to be more convenient and cost effective. A novel mobile phone-based system was created, which is able to process and store oximetry data securely. The mobile phone is linked via an adaptor to a commercially available oximeter. A patent was filed with the Intellectual Property Office of Singapore for this technology (application number 10201500967S – "Telemedicine Oximetry System). We are not aware of the existence of such applications commercially.

We conducted a prospective observational feasibility study of surgical patients at risk of OSA to determine the utility of a novel smart phone

Edwin Seet, MBBS, MMed, FAMS ; Cheryl Saw Jiayu, MBBS ; Kwong-Ming Leong, BMed MD ; Chandra M. Kumar, MBBS, FFARCS, MSc, FRCA, EDRA, FAMS.
Department of Anesthesia, Khoo Teck Puat Hospital, Singapore
Corresponding Author : Dr Cheryl Saw Jiayu, Khoo Teck Puat Hospital, Yishun Central 90, Singapore 768828.
Phone : +6566022317, Fax : +65660237648
E-mail : cheryl.saw@mohh.com.sg

ES, CS, LKM and CMK have made substantial contribution to the manuscript in drafting the article or revising it critically for important intellectual content, final approval of the version to be published. They agree to be accountable for all aspects of the work.

Paper submitted on July 30, 2020 and accepted on October 4, 2020
Conflict of interest : None

application for OSA detection and calculation of the cumulative time of oxyhemoglobin desaturation. Informed consent was obtained for all participants and institutional research board endorsement was given (DSRB reference 2017/00891) by the chairperson and members of Domain D (Anesthesia), National Healthcare Group Domain Specific Review Board, Nexus @One-North (South Tower), No. 3 Fusionopolis Link, #03-08, Singapore 138543. The inclusion of subjects into the study started on December 01, 2018 and ended on July 01, 2019.

A smart phone (Xiaomi Redmi 2, model number 2014817) with an Android operating system (5.1.1, LMY47V) was loaded with a novel application for OSA detection. This was connected to a commercially available oximetry finger probe (Masimo, iSpO_2) to create a novel phone application-based pulse oximetry system. Data from the pulse oximeter was directly transferred to the smart phone in real time, with processing and calculation of data conducted on the phone application itself. Data retrieval can either be conducted directly from the phone, or online via a secure connection. The mobile phone application is configured to upload data securely and wirelessly through the respective hospital intranet Wi-Fi, including but not limited to, WPA2 Enterprise or higher, to a backend system in a cloud or to a designated server in a secure hospital WLAN or LAN. For this study, all data was retrieved directly from the phone itself to protect patients' confidentiality and to avoid loss of data in the event of limited internet connection. The framework of this phone app-based pulse oximetry system was designed based on current literature on the use of nocturnal oxygen desaturation index for surgical patients with suspected OSA (4).

This phone application-based pulse oximetry system was compared with a commercially available proprietary Level IV pulse oximeter wristwatch (Pulsox-300i, Konica Minolta Sensing Inc, Osaka, Japan). The aim of the study was to determine the feasibility and accuracy of the novel smart phone application attached to a finger oximetry probe for OSA detection and calculation of cumulative time of oxyhemoglobin desaturation during sleep.

Patients planned for elective surgery were recruited if they were suspected to be at risk of OSA, by scoring at least 3 out of 8 or more (i.e. at risk of OSA) using the STOP-Bang screening tool (5). Seven male patients and 1 female patient were recruited between December 2018 and June 2019. The smartphone app-based oximetry system and the Pulsox-300i were applied to the same hand of study participants just before bedtime and were removed the next morning. Data compared from both devices included the heart rate, lowest O_2 saturation, cumulative time of oxyhemoglobin desaturation with SpO_2 < 80% (CT 80%) and 90% (CT 90%), and the number of episodes per hour of oxygen desaturation of ≥4% lasting for at least 10 seconds, defined as the oxygen desaturation index (ODI 4%). For the Pulsox-300i oximeter, the ODI 4% was calculated using a ≥4% decrease in average SpO_2 values for each patient in the preceding 120 seconds. The ODI 4% was automatically calculated via an in-built analysis tool in the phone app-based pulse oximeter (Figure 1). For both devices, the CT 80% and CT 90% were manually calculated from downloaded data.

The Pearson's correlation coefficient was used to assess the strength of data association between the Pulsox-300i and the novel smartphone

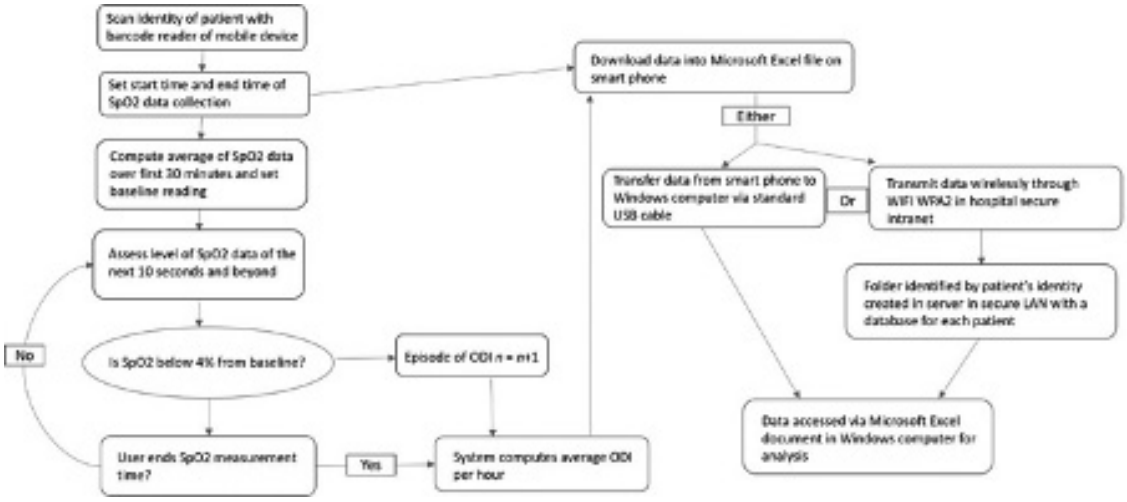

Fig. 1. – Novel mobile phone application-based pulse oximetry system.

Table 1

Parameters measured from the smartphone app-based oximetry system and the Pulsox-300i

	Masimo	Pulsox-300i
HR (beats/min)	74 ± 12	74 ± 12
Lowest SpO_2 (%)	81.5 ± 9.8	74.4 ± 8.2
CT 90% (% of sleep time)	1.1 ± 0.9	1.7 ± 1.8
CT 80% (% of sleep time)	0.4 ± 0.6	0.4 ± 0.3
ODI 4%(% of oximetry time)	7.1 ± 5.5	13.9 ± 10.4

HR = Heart rate, SpO_2 = Oxygen saturation, CT 90% = Cumulative time with SpO_2 < 90% expressed as percentage of sleep time, CT 80% = Cumulative time with SpO_2 < 80% expressed as percentage of sleep time, ODI 4% = number of episodes per hour of oxygen desaturation of ≥ 4% lasting for at least 10 seconds expressed as percentage of oximetry time.

oximetry system. The Bland-Altman method was also used to determine agreement of both devices. The limits of agreement were reported based on standard deviation. Data analysis was performed using GraphPad Prism (Version 8.4.2 for Windows, GraphPad Software, La Jolla California USA). As this was a feasibility study, no sample size calculation was done.

Of the 8 patients recruited, 2 patients had no OSA, 4 patients were found to have mild OSA and 2 patients found to have moderate OSA. The smartphone app-based finger probe was dislodged during sleep for 1 patient (no OSA), and the Pulsox-300i finger probe was dislodged during sleep for 1 patient (mild OSA). The age range of patients was between 40 to 72 years, with a mean age of 60 ± 10 years. The data obtained from both devices is summarised in Table 1.

Cumulative time of SpO_2 < 90% (in percentage of number of hours of recorded oximetry time) was 1.1 ± 0.9% for the smartphone group and 1.7 ± 1.8% for the Pulsox-300i group (Table 1). Cumulative time of SpO_2 < 80% (in percentage of

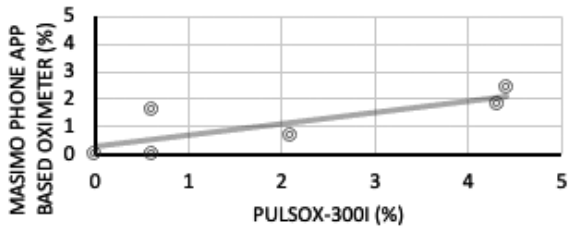

Fig. 2. – Percentage of overall sleep time with SpO_2 < 90% measured by the Pulsox-300i versus the smartphone app-based oximetry system.

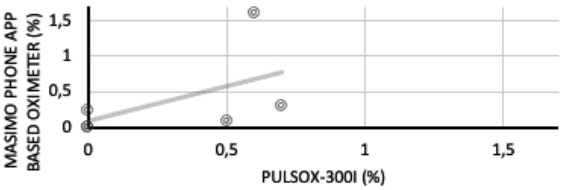

Fig. 3. – Percentage of overall sleep time with SpO_2 < 80% measured by the Pulsox-300i versus the smartphone app-based oximetry system.

number of hours of recorded oximetry time) was 0.4 ± 0.6% in the smart phone group and 0.4 ± 0.3% in the Pulsox-300i group (Table 1). The Pearson's correlation coefficient for CT 90% was 0.8 (Figure 2) and that of CT 80% was 0.6 (Figure **3**), indicating a high positive correlation for both devices in the calculation of CT 90% and a moderate positive correlation in the calculation of CT 80%.

The CT 90% and CT 80% was plotted using the Bland Altman method to measure agreement between both devices (Figure 4). The mean bias for the CT 90% as a percentage of recorded oximetry time was 0.9067% {Limit Of Agreement (LOA) : -1.625 to 3.438%} while the mean bias for CT 80% as a percentage of recorded oximetry time was 0.0917% (LOA : -0.4135 to 0.5968%).

There were several limitations to the study identified during the data collection process. Finger probe dislodgement was a common occurrence

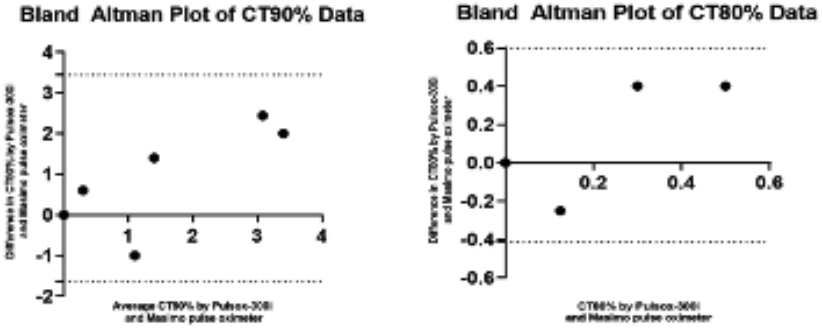

Fig. 4. – Bland-Altman plots for CT90% and CT80% data from the Pulsox-300i and Masimo pulse oximeter. The dotted lines represent the 95% limits of agreement calculated from the data obtained.

in 12.5% of patients and was shown to affect the accuracy of data collected. It was difficult to monitor compliance to finger oximetry overnight and dislodgement could only be identified during data retrieval the following day. Patients also needed to be educated on the use of these sleep tests to ensure compliance overnight, which may prove to be difficult in patients who lack capacity to do so, including patients with dementia or other neurological pathology.

Additionally, overall sleep time was not measured in this study as patients were not evaluated for onset and offset of sleep, or periods of wakefulness during the night. As such CT 90% and CT 80% values were interpreted based on the number of recorded oximetry hours rather than each patient's sleep time.

In this study, it was shown that 75% of the patient cohort had unrecognized OSA, in keeping with previous large sample size publications (1). Interclass correlation between both devices showed moderate agreement for measured cumulative time of $SpO_2 < 90\%$. Based on the Bland-Altman analysis, all patients were within the LOA for both devices with a low mean bias. As such, the novel smartphone application-based oximetry system may play a role in perioperative OSA screening and detection. We propose that this smartphone application to be used by medical professionals as a quick screening tool in conjunction with current scoring systems like the STOP-Bang score to assess a patient's risk of OSA prior to surgery. These patients can then be referred early for an eventual initiation of continuous positive airway pressure (CPAP) therapy in order to reduce the risk of post-operative respiratory complications. Data from the phone app-based pulse oximeter can also be more readily accessed as compared to current commercially available level IV sleep devices which require proprietary hardware for data accessibility. This easy accessibility also enables patients to use the phone oximeter to assess their risk of OSA and seek medical attention early if indicated. This may potentially be useful in reducing the burden placed on hospital resources for PSG studies and could also be a more convenient option for patients who may wish to reduce their number of hospital visits pre-operatively.

Acknowledgements

The authors would like to acknowledge the contributions by Dr Daniel Chia and Ms Audris Chia for the creation of the mobile phone application and data collection respectively. The authors declare they have no conflict of interest and no financial interest in the products included in this study. The mobile phone application creation and study was supported by the Alexandra Health Enabling Grant FY 2017 (AHEG1703) – limited from 2017-2019.

References

1. Chan M., Wang C., Seet E., Tam S., Lai H. and Chew E., et al. 2019. Association of Unrecognized Obstructive Sleep Apnea With Postoperative Cardiovascular Events in Patients Undergoing Major Noncardiac Surgery. JAMA. 321(18):1788.
2. Ferber R., Millman R., Coppola M., Fleetham J., Murray C. and Iber C. et al. 1994. Portable Recording in the Assessment of Obstructive Sleep Apnea. Sleep. 17(4):378-392.
3. Thornton A., Singh P., Ruehland W. and Rochford P. 2012. AASM Criteria for Scoring Respiratory Events: Interaction between Apnea Sensor and Hypopnea Definition. Sleep. 35(3):425-432.
4. Chung F., Liao P., Elsaid H., Islam S., Shapiro CM. and Sun Y. 2012. Oxygen desaturation index from nocturnal oximetry: a sensitive and specific tool to detect sleep-disordered breathing in surgical patients. Anesth Analg. 114(5):993-1000.
5. Chung F., Abdullah HR. and Liao P. 2016. STOP-Bang Questionnaire: A Practical Approach to Screen for Obstructive Sleep Apnea. Chest.149(3):631-638.

(Acta Anaesth. Belg., 2020, 71, 111-121)

Organizing a safe operating room during a pandemic. What did we learn from COVID-19?

S. Casaer (*), T. Sebrechts (**), P. Van Houwe (*), W. Rattenberry (***)

Abstract : During the COVID-19 pandemic, multiple guidelines have been issued on hospital safety and protection measures to prevent transmission to healthcare workers and to other patients. The operating room is a high-risk environment where enhanced precautions are required. The guidelines differ and practical implementation between hospitals can also vary, according to interpretation and budget. Staff at risk may question if the local policies are sufficient and correct. This article provides an overview and theoretical background to the additional safety measures required in the operating room during a viral pandemic like the COVID-19 pandemic. This may serve as a touchstone and tool for anesthetists and OR managers.

Key words : Safety ; coronavirus ; breathing circuit filter ; PPE ; OR management.

Introduction

During early 2020, healthcare institutions across Europe have been inundated by patients suffering from coronavirus disease (COVID-19). It was caused by a novel coronavirus (2019-nCoV, later SARS-CoV-2) originating in Wuhan, China. The high number of patients requiring long hospital and ICU admission placed an enormous pressure on healthcare systems. Italy became a devastating European example, where the pandemic hit early and hard, making health care providers struggle with shortage of logistics and supplies and exhaustion of staff due to illness.

All European countries started to prepare and organize for an impending disaster. Hospitals invested in reorganization of services and expansion of ICU beds to prepare for high numbers of patients suffering from COVID-19. Safety guidelines were implemented to protect against cross-contamination of staff and logistics, and staff were urgently prepared for work in emergency or ICU care. Incredible organizational work has been performed in a very short time interval.

With this there has been a huge tsunami of information for health care workers, often updated daily. Leading international and national organizations, including the World Health Organization (WHO), the European Society of Intensive Care Medicine (ESICM), the European Centre for Disease Prevention and Control (ECDC), the Centers for Disease Control and Prevention (CDC), alongside national societies have provided guidelines. However, the finetuning and practical implementation has varied among hospitals. This has resulted in a feeling of uncertainty and doubt amongst caregivers with the Chinese and Italian experience emphasizing the high risk of transmission to health care workers (HCW).

In the early organizational phase hospital crisis teams focused on the emergency department, hospital admission units and intensive care expansion. Providing a safe working environment in the operating room for patients and staff is also of paramount importance, with high numbers of infectious symptomatic, as well as infectious asymptomatic patients, presenting for urgent and emergency surgery.

This article summarizes the technical details needed for organizing a safe operating room, not only during this pandemic, but it can give guidance in case of future pandemics.

Transmission

Understanding the mode of transmission of the etiologic agents is essential when preparing

Sari Casaer, MD EDRA ; Tom Sebrechts, MD ; Patrick Van Houwe, MD ; William Rattenberry, MD EDRA
(*) Department of Anaesthesiology and Intensive Care, GZA Ziekenhuizen. Wilrijk, Belgium
(**) Anaesthetic Registrar, University Hospital Antwerp, Belgium
(***) Nottingham University Hospitals, UK
Corresponding author : Tom Sebrechts, Kardinaal Mercierlei 21 bus 401, 2600 Berchem, Belgium
Email : tom.sebrechts@student.uantwerpen.be ;

Paper submitted on May 14, 2020 and accepted on August 25, 2020
Conflict of interest : None

the working environment. The novel coronavirus SARS-CoV-2 is mainly transmitted through large respiratory droplets and contact transmission (with infected persons, objects or surfaces), but other modes of transmission have also been proposed (1-3). Sneezing or coughing produces mainly large droplets >5mm up to 1m (3 feet) around a patient. Examples of other pathogens spread in this way are Influenza, RSV and adenoviruses. Because the droplets tend to fall to the ground quite quickly, measures to control air flow are not indicated (4). Airborne spread means small residuals of droplets, 'droplet nuclei' are suspended in the air, subsequently dry and produce particles ranging in size from 1-5 μm, containing possible viable micro-organisms e.g. Mycobacterium tuberculosis, Varicella Zoster virus, that can remain suspended in the air and be transported over longer distances (4, 5). Droplet nuclei can be deposited into the lower respiratory tract when inhaled, in contrast to larger droplets.

Pathogens normally transmitted only by contact or by droplets, can become airborne under certain conditions, during so-called 'aerosolization'. This requires high velocity flows of liquid and air. These accelerated flows can be generated during invasive medical interventions, such as e.g. in- and extubation, bronchoscopy or tracheal suction. Such procedures are described as 'aerosol generating procedures – AGPs'(5, 6). Very few viruses can become airborne, thus meaning they remain in an infective state in droplet nuclei caused by aerosol, and factors facilitating this are unknown. One requirement is a sufficient 'viral load' suspended in the aerosolized particles. In the context of the SARS-CoV-2, airborne transmission may be possible but this is controversial (7, 8). As this is a new virus, evidence on possible modes of transmission had to be obtained during the course of the pandemic itself. In our opinion, safety measures against the most invasive way of transmission possible should be taken until proven otherwise. As such during the first phase of the COVID-19 pandemic protection against airborne transmission is advised when performing AGP's as there is no clear evidence that the SARS-CoV-2 doesn't spread airborne.

Likewise the WHO advises precautions against droplet and contact transmission, and against airborne transmission during and shortly after AGP's (2).

Viral RNA has also been detected in feces, the significance of this finding has yet to be determined. Blood-borne transmission is not regarded an important source of transmission (9).

Operating Room Management

During a pandemic the management and protection of medical personnel is of great importance since the amount of available HCW in the operating room is limited. Obviously, prevention of transmission to other admitted patients is of upmost importance as well.

Performing cases of a confirmed infected patient in a dedicated operating room is strongly advised, as all preparations to prevent cross-contamination can be made well in advance. This operating room should be easily accessible and ideally have a preparation room for donning and doffing personal protective equipment. All unnecessary equipment, as well as the anesthesia tray, should be removed from the OR. An 'outside' nurse should be appointed to hand over supplies if needed. Unremovable equipment can be covered with plastic, water-resistant sheets. As the pandemic evolves it may become necessary to expand the number of dedicated OR's.

Different access ways to the operating room for infected and non-infected patients should be provided. While waiting for surgery, contaminated patients have to be placed in an isolation room, preferably as close as possible to the dedicated operating room with the least passage through non-contaminated parts of the hospital. If possible recover the patient in the operating room or otherwise in an isolation room (10).

Aim for as few different people as possible working daily in the operating room (e.g. longer shifts) to reduce the use of surgical masks and to reduce potential exposure. This may mean interns or residents are excluded and teaching opportunities missed.

Do 1 case in an OR, followed by terminal cleaning, with the second case in another OR and switch between OR's (10).

If the surgeon (proceduralist) will be operating later in the day and is scheduled for only 1 procedure, provide notification when there is the start of closure of the preceding case being done by the anesthesia and nursing team. This communication reduces their total exposure time in the OR and should not limit workflow if the preceding patient will be recovered in the OR by the anesthesiologist (10).

Local policy should include protocols to guide management of patient flows and use of safety measures in the OR. The management of patients with uncertain infective status (e.g. patients under investigation, asymptomatic patients during the peak of a pandemic) should be clearly guided by local protocols during different stages of the

pandemic, to avoid confusion and consequently a risk of 'protocol tiredness'.

Operating Room Preparation

Manipulating the airway during induction and awakening of general anesthesia is associated with aerosol-generation. The anesthesia working space contains numerous surfaces that can harbor droplets thus serving as reservoirs for the virus if proper droplet precautions or proper decontamination processes are not followed (11). Moreover, laparoscopy, pulse lavage and electrocauterization may also lead to aerosolization of blood borne viruses (9, 12, 13).

Laminar flow/Negative pressure room

Several organizations e.g. ASA, ECDC, CDC WHO cite that AGP's should be performed in a negative pressure room (AIIR, airborne infection isolation room), to prevent airborne contamination of surrounding spaces. Negative pressure is created and maintained by a ventilation system that allows extra air to enter the isolated room by differential pressure and be exhausted directly to the outside or be filtered through a high-efficiency particulate air (HEPA) filter directly before recirculation. Negative pressure function for OR's is not universally present in European institutions. The most commonly used OR ventilation systems are Laminar Air Flow (LAF) systems, by which air is supplied in a parallel manner through the OR. This is achieved by providing large volumes of air with a uniform flow field over the clean zone (Fig. 1) (14). The flow can be in a vertical direction (from ceiling to floor) or in a horizontal direction (between walls). The idea is to swipe away or wash out any micro-biological contamination from the surgical zone and prevent bacteria-carrying particles from being encountered in the wound area (15).

The WHO states AGP's should be performed "in an adequately ventilated room – that is, natural ventilation with air flow of at least 160 L/s per patient or in negative-pressure rooms with at least 12 air changes per hour and controlled direction of air flow when using mechanical ventilation." (2).

If a negative pressure setting is not available, it is unclear if LAF should be turned off. This would lower the chance of blowing contaminated air into the surrounding corridor, but at the same time turning off LAF impedes refreshing the air inside of the OR, which holds a potential risk of augmenting surgical site infections. Chinese experience advises

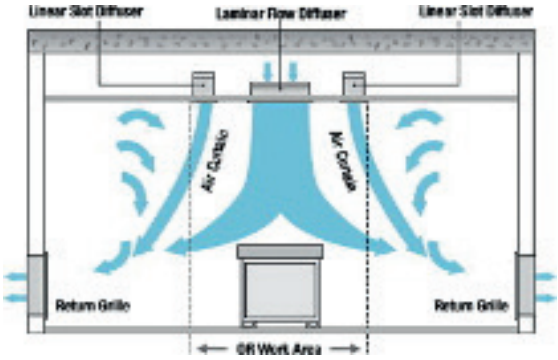

Fig. 1 – Diagram of a Laminar Air Flow system (10).

to switch off positive pressure systems and air conditioning (16, 17). Limiting door openings to the absolute minimum in an OR with LAR turned on is strongly advised (16), especially during and after AGP, allowing enough time for the air inside the OR to be refreshed. Knowledge of the number of air exchanges per hour at your local institution is essential, and the safety period around an AGP should take at least 5 air exchanges to diminish the viral load to <1% of the initial load (9).

Cleaning

Viral pathogen survival on environmental surfaces extends for several days. SARS-CoV-2 can survive for at least 3 days on a variety of materials commonly encountered in the OR (e. g. stainless steel, plastic) in case of a very high viral load. If the viral load is below 10,000 particles, which is closer to reality, the virus persists not more than 5 minutes on any surface (10, 18). Moreover, persistence of virus on a surface does not mean one can be contaminated.

Nevertheless cleaning and disinfection procedures are of paramount importance (with cleaners and water, followed by applying an EPA-registered hospital-grade disinfectant for the indicated contact time). The EPA (US Environmental Protection Agency) website publishes a list on disinfectants registered for use against SARS-CoV-2 (19). This can be extended to other viruses.

Anesthesia ventilator

The anesthesia ventilator is at specific risk for contamination by respiratory viruses, with expired gas returning to the ventilator and re-used in low-flow systems. Internal decontamination of the ventilator system is a difficult process and cannot be readily performed. Therefore all measures should be taken to avoid viral spread inside. A breathing circuit

filter (preferable a heat and moisture exchanging (HME) filter) with a high viral filtration efficiency (VFE) should be used between the Y-piece of the breathing circuit and the endotracheal tube. Moreover installation of a second filter between the expiratory limb of the breathing circuit and the anesthesia machine is advised (16, 20).

A wide range of different filters and producers are on the market and technical details of filters available at your own institution should be reviewed. Almost all mention high bacterial and viral filtration efficiency (at least 99,99%). A VFE of 99.99% means that only one particle in 10,000 (10^4) will pass through the filter under standard test conditions that control flow rate at 30 L/minute. Increased flow rate reduces the VFE (20). It is not exactly known what VFE is needed to prevent passage of SARS-CoV-2 particles from the patient to the anesthesia machine.

There are two main types of filters based on the working mechanism : mechanical (pleated) and electrostatic filters. The term 'High Efficiency Particulate Air' filter (HEPA) is used for filters that remove at least 99.95% (European Standard EN 1822) or 99.97% (US) of particles whose diameter is equal to 0.3 µm, and does not indicate the mechanism of filtration (mechanical or electrostatic).

The diameter of SARS-CoV-2 is around 0,12 mm but transported in droplets or droplet nuclei with a diameter of 1-5 µm.

Both filter types rely to a certain extent on electrostatic charge for their filtering capacity. Electrostatic filters have a low density of fibers and a high charge. Mechanical filters on the other hand consist of a hydrophobic surface with a high density of fibers, which may cause a slightly higher resistance to air flow. Pleating the surface lowers this resistance. The filtration performance of mechanical filters is said to be superior (21, 22) (Fig. 2). They are also slightly more expensive.

An important difference between electrostatic and mechanical filters is their resistance to humidity.

Humidification of air is important during artificial ventilation to maintain mucociliary function. This is particularly important during long-term intensive care ventilation. In the anesthesia setting, humidification is achieved by using low fresh gas flow in a circle breathing system, which consequently allows rebreathing of exhaled air that passes through a CO_2-absorber where water vapor is produced. This ensures for enough humidification during short procedures. For longer surgeries HME filters are positioned at the proximal end of the endotracheal tube (ETT).

Breathing filters can become saturated by condensation liquid from the breathing circuit or by secretions of the patient (especially during prone positioning). This causes a rise in resistance to airflow in the circuit and high-pressure alarms may be activated. Pressure alarms are usually set at 30-40 cmH_2O. Filters should be able to withstand this pressure without passing possibly contaminated liquids from the patient into the breathing circuit or reverse. The German Society of Hospital Hygiene and the German Society for Anaesthesiology and Intensive Care recommend the use of filters that can withstand a pressure of 60 hectopascals (approximately 60 cm H_2O) to allow a margin of safety (23). For electrostatic filters the pressure required to force liquid through is lower than this threshold (23), so possible contamination of the expiratory limb can occur during episodes of high airway pressure. On the contrary, when mechanical filters are obstructed by water, no fluid particles can get through and high breathing circuit pressures will be noted.

In the setting of the highly contagious SARS-CoV-2, the use of a mechanical HEPA filter between the Y-piece and the ETT is consequently advised (11).

To protect the ventilator against the minimal residual (0,01 or 0,001) percentage of viral particles in the expiratory limb, a second filter may be used between the expiratory limb of the breathing circuit and the ventilator itself, to amplify the effectiveness of the HME filter (11). This argument is emphasized in case of electrostatic filter use at the Y-piece due to lack of HEPA filters. This second filter doesn't have to be heat and moisture exchanging (HME).

It should be noted that whilst there has been concern regarding the 0,01 or 0,001% of leakage on the filtering capacity of breathing circuit filters, the respiratory masks of the staff (FFP2 or FFP3) filter 'only' 94% and 99% respectively (Fig. 2). The filters do handle directly expired air from patients, in contrast to the breathing masks of HCW, that filter droplets and 'aerosolized' particles from environmental air.

The necessity of changing breathing circuits between patients is unclear. If a high-quality mechanical breathing filter is installed, soiling of the circuit should be minimal. A study in which the levels of contamination were measured in anesthesia breathing systems used for several patients with an electrostatic filter between the patient and the breathing system ; breathing system contamination was found in 5.6% after 72h (22, 24). Therefore the breathing circuit should be replaced

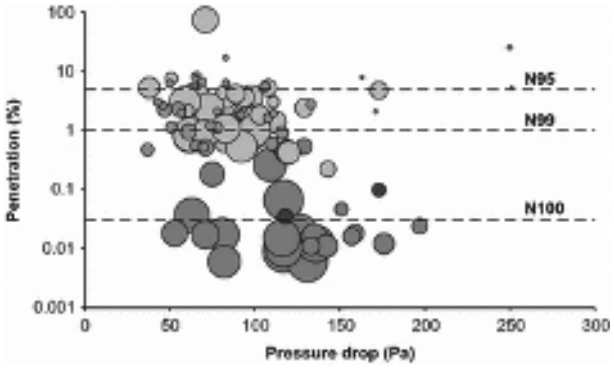

Fig. 2. — Penetration through filters against pressure drop. The size of each 'bubble' is related to the internal volume of the filter. N95, N99 and N100 refer to the three classes of respiratory protective devices when challenged with sodium chloride : N95, better than 95% filtration efficiency (<5% penetration) ; N99, better than 99% efficiency (<1% penetration) ; N100 better than 99.97% efficiency (<0.03% penetration). Adult electrostatic filters : paediatric electrostatic filters ; adult pleated filters ; paediatric pleated filters. All pleated filters were at least N99, no electrostatic filters were N100, some electrostatic filters were not N95 (18).

after every contaminated patient, especially since there is concern of mixture of in- and exhaled air in the Y-piece.

Respiratory gas sampling

Respiratory gas sampling for analysis should be performed after filtering the exhaled air through a high-quality filter (cfr. supra), to prevent viral transmission to the gas analyzer (Fig. 3). Some machines redirect the gas sample for reuse in the breathing circuit, while others direct it to the scavenging system. In the anesthesia setting, directing the analyzed gas to the scavenging system is preferred, in case of reuse in the breathing circuit additional filtering should be present in the water trap. The water trap should be changed before starting non-infected case with this ventilator.

In contrast, when the anesthesia machine is used as an ICU ventilator and scavenging is not present, gas sampling should be disabled or reprogrammed by qualified personnel for redirection to the breathing circuit, to prevent contaminating environmental air. As an alternative, an epidural drug-injection filter can be placed on the gas sample port of the breathing circuit filter before connecting the gas sample line, although this may diminish the quality of the capnograph (20).

Personal protective equipment (PPE)

All personnel involved in the care of a positive patient should wear sufficient protective equipment

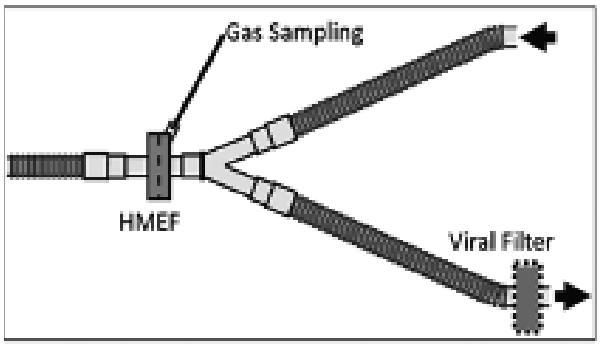

Fig. 3 – Preferred filter and gas sampling configuration (18).

and apply appropriate hand hygiene. National and international guidelines have been published, but practical implementation of PPE differs among centers, due to differences in interpretation and resource. Shortage of supplies during the COVID-19 pandemic obliged further variations. Advises are guided by the mode of transmission in a specific setting, and safety requires protection against the most invasive mode of transmission possible. In the setting of treatment of a COVID-19 positive patient in an OR, this means protective measures should be taken against airborne transmission.

When we look at the guidelines published by the ECDC on PPE for COVID-19 (1, 25), recommendation includes body protection (long sleeved water-resistant gown), mask (filtering face piece FFP3 (N99) or FFP2 (N95) according to European standard 149), eye protection (well fitted goggles or face shield) and gloves.

Concerning the FFP masks ECDC recommends always using an FFP3 for aerosol generating procedures, as FFP3's filtering capacity for airborne particles is 99%, in comparison to 94% for FFP2 (1). WHO states using an FFP2 (2). The confusion on this topic rose dramatically when several centers reported test results revealing insufficient filtering capacity of newly delivered masks during the COVID-19 pandemic, despite recording FFP2 on the technical details.

FFP2 or FFP3 masks do not fit each face morphology. HCW need to be aware of the fact that these masks can be totally useless if not adequately adapted. A quantitative face fit test before clinical use is advisable.

During surgery, when the airway is protected by an ETT and no AGP takes place, a surgical mask is probably sufficient, but to avoid confusion it may be safer to keep wearing the FFP2.

The ECDC defines body protection as a long-sleeved impermeable gown, referring to its technical guidance document on PPE for treatment

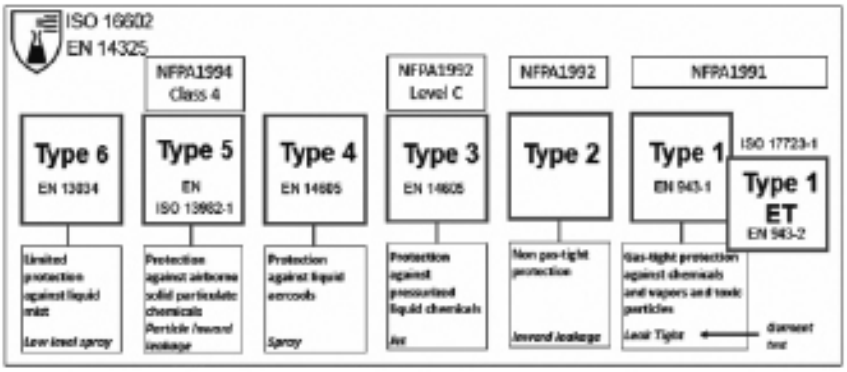

Fig. 4. — Overview of different global standards (EN: European Norm, ISO : International Organization for Standardization, NFPA : National Fire Protection Association) (24).

of 'Infectious Diseases of High Consequence' (IDHC). This states that a coverall is preferred, which makes it debatable. Probably the importance of the material of the body protection outweighs the choice between gown of coverall, as both have pro and cons. Coveralls implicitly cover more body parts, including head, neck and lower legs, but are more difficult for doffing without the risk of self-contamination. WHO explicitly states that a coverall is not necessary (2).

The quality norms on protective clothing are difficult to interpret as different classifications exist (26, 27). Protective clothing in medical settings should mention the European quality Norm (EN) 14126, which indicates appropriateness to protect against biohazards (air- or bloodborne infective agents). Functional details, such as taped seams, attached hoods, or covered zippers are not defined by EN 14126. Therefore, these specifications need to be checked and specified.

Reference to the classifications used in chemical industry (EN14325 and ISO 16602) is often mentioned, which grades leak tightness to chemical exposure in 6 Types (Fig. 4).

The addition of the letter 'B' to the Type (e.g. Type 5-B) indicates that the material is certified for biological contaminants according to EN 14126. This can also be indicated by the pictogram in Fig. 5.

The ECDC states that fabric of class 3B is good for working with IDHC.

The label 'Category III' implies annual third party confirmation of the certificate validity, which is mandatory for protection against dangers that seriously harm health.

EN 14126 comprises several testing methods for permeation of different biological substances. These can be separately indicated, and are graded, with the highest class indicating the best protection,

Fig. 5. — EN14126 Protection against biohazards.

Table 1

EN 14126 testing methods for permeation of biological substances

ISO 22610	microbial permeation of liquids	grade 1-6
ISO 22611	microbial permeation of aerosol	grade 1-3
ISO 22612	microbial permeation in dry conditions	grade 1-3
ISO 16603	pressure needed for permeation of blood borne pathogens and synthetic blood	grade 1-6
ISO 16604	pressure needed for permeation of blood borne viruses	grade 1-6

e.g. ISO 16604 grades the protection against blood borne viruses. (Table 1)

In the operative setting surgical sterile gowns are also required. Due to the shortage of protective clothing during the COVID-19 pandemic, surgical gowns also could be used outside the OR, on the COVID-19 wards. Those gowns are certified by a different norm EN 13795, which focusses on the protection of the patient, in contrast to the before mentioned EN 14126 which implicates protection of the medical staff, thus the direction in which the sample is brought into contact with the contaminating agent during the test is opposite. Although making comparison difficult this doesn't mean surgical gowns are less protective.

EN13795 mostly doesn't mention testing method ISO 16604 for viral penetration. Surgeons wonder if it is necessary to wear a protective gown

under the surgical sterile gown. If the sterile surgical gown is adequately reinforced or fluid resistant, wearing a protective gown underneath is probably not necessary. The WHO states that aprons should be used if gowns are not fluid resistant (2).

The US hands a different classification (AAMI : Association for the Advancement of Medical Instrumentation) for medical protective apparel as well as for surgical gowns. For protection against viral penetration, the highest AAMI level 4 (test ASTM F1671) is required.

During the COVID-19 pandemic a world-wide concern was expressed on shortages of adequate PPE for healthcare workers. Because of this pressing shortage engineers started to design and produce alternatives. E.g. the 3D printing of an adaptor to connect a HEPA filter to the re-usable water-sealing Decathlon Easybreath Subea diving mask, as an alternative to an FFP2 mask for protection of HCW (Fig. 6). Keeping in mind the different filtering capacities of FFP2 and HEPA filters, this may even be a superior alternative. This system hasn't been biomedically certified as concerns are expressed that the water-sealing capacity of these masks depends partially on external pressure caused by the water during diving, and due to the necessity of closing the water purge valve of the mask before use as a filtering face piece.

This text describes the ideal technical details of PPE components, but reality obliges to accept that these high standards may not always be fulfilled.

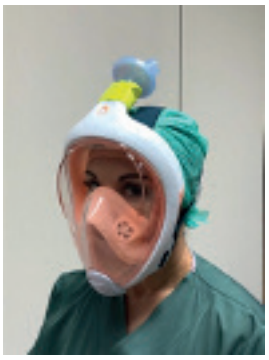

Fig. 6. — Experimental face guard. Adaptor for Decathlon Easybreath Subea mask designed by A. De Beir,, PhD Faculty of Engineering Vrije Universiteit Brussel ICW. Dr. B. Geniets MD, GZA Ziekenhuizen.

Aerosol generating procedures in the operating room

Aerosol generating procedures (AGPs) include endotracheal intubation and extubation, bronchoscopy, open suctioning, manual ventilation before intubation, disconnecting the patient from the ventilator (or actions with augmented risk on disconnection e.g. physical proning of the patient), tracheostomy, and cardiopulmonary resuscitation. For some procedures there are conflicting data on whether they have to be regarded as infectious aerosol generating or not, e.g. administration of nebulized treatment and high-flow nasal oxygen (3, 9, 17, 28).

Also certain surgical procedures carry a risk on aerosolization of respiratory virusses, e.g. thoracotomy and pneumothorax exsufflation. The air evacuated from the pneumoperitoneum during or after laparoscopy can also lead to aerosolization of blood borne viruses (13). No clear evidence exists on the risk of laparoscopy in COVID-19 patients, but care should be taken and laparoscopy should only be performed when strictly indicated. The Society of American Gastrointestinal and Endoscopic Surgeons has published practical safety measures on laparoscopy, surgical indications and electro-cauterization (12).

As AGPs are increasingly being recognized as an important source for nosocomial transmission of emerging respiratory viruses, protection measures are required (5). During the SARS outbreak, intubation was one of the independent risk factors for super-spreading nosocomial outbreaks affecting many healthcare workers in Hong Kong and Guangzhou, China (28).

Personal protective equipment should be used as mentioned above : a non-sterile long-sleeved gown with adequate quality norm, FFP2 (N95) masks or equivalent, eye protection (face shield or well fitted goggles) and gloves, preferably a double pair of gloves, well covering the wrists. A surgical hat is also recommended and is usually worn in the OR. After the procedure at least gloves and if stock allows also the gown are switched and appropriate hand hygiene is applied, before moving on with the surgery.

If there is a shortage of FFP2 (N95) masks or other PPE components it is recommended that they are prioritized for AGPs. To preserve supplies and contamination risk, the number of persons present in the room during AGP's should be limited to the absolute minimum required for the patient's care and support.

Intubation / Extubation

Several instructions on intubation and extubation of COVID-19 patients have been published and all are fairly similar (2, 3, 11, 16, 19, 29, 30). In

the setting of the operating room, intubations will be mostly (semi-)elective and permit adequate planning and preparation of safety measures, according to the same guidelines. ICU patients on high flow nasal oxygen or non-invasive ventilation needing surgery may be best intubated before transfer to the OR.

Standard monitoring, intravenous access, instruments, drugs, ventilator, and suction should be prechecked. Rapid sequence induction (RSI) is advised, with 3 minutes of preoxygenation with 100% oxygen (31). Pre-oxygenation can be performed with a Bag Valve Mask device with positive end expiratory valve and a viral filter, if available. It is recommended to keep a good facemask seal with both hands, while making sure not to deliver any positive breaths. Wet gauze can be put around the mouth and nose to block secretions (16). The utilization of a high flow nasal canula (HFNC) in the ICU does not increase either dispersion or microbiological contamination into the environment when compared to oxygen therapy with a mask. The patient being able to wear a surgical mask on top of HFNC, in order to reduce the aerosol transmission during coughing or sneezing, represents an additional benefit (32). The use of HFNC is rarely applied in the OR and to date there are no publications of its use in contaminated patients prior to induction. If possible, it seems more appropriate to avoid HFNC in the OR considering the face mask for induction has better sealing capacities. Induction and relaxant medications should be administered at a sufficient dose in order to prevent cough or gag reflex during the procedure (29, 30). RSI may need to be modified if the patient has very high alveolar–arterial gradient and is unable to tolerate 30 seconds of apnea or has a contraindication to a neuromuscular-blocking drug. If manual ventilation is required, small tidal volumes with low pressure should be applied. The intubation technique which can reduce the number of attempts at endotracheal intubation, the duration of the procedure and the proximity between the operator and the patient, should be prioritized. Therefore the use of video-guided laryngoscopy is suggested over direct laryngoscopy, if available. Moreover, the endotracheal intubation should be performed by the healthcare worker who is most experienced with airway management. In a failed airway scenario, attempts should be made to establish a surgical airway immediately. Avoid awake fiberoptic intubation unless specifically indicated.

Connecting the HEPA-filter on the ETT before insertion is advisable to prevent contamination in case of coughing after insertion.

The ETT should be positioned at a predetermined depth and secured properly. No breaths should be delivered until the cuff is inflated. Avoid auscultation attempts to prevent instrument contamination, instead assessing for bilateral chest rise and end-tidal capnography waveform.

A plastic transparent sheet can be placed over the patient's head and chest during the procedure to prevent droplet spread, although this may limit visibility and may be difficult to dispose without contact transmission.

All contaminated instruments should be placed in a bag for immediate disposal and/or decontamination.

As RSI is always applied when performing emergency intubation, the same measures as stated above are advised when an emergency intubation is necessary in a contaminated patient.

Cough is a common event following premedication with an opioid such as fentanyl (given prior to induction of anesthesia) and can be prevented by a single intravenous dose of lidocaine (0.5 mg/kg) (33). In addition, coughing and bucking are also prevalent events during extubation. Therefore also during extubation a plastic transparent sheet can be placed over the patient's head and chest. Full PPE should be worn by the HCW and the patient's face mask should be kept close so that it can be put on shortly after extubation. Usage of endotracheal aspiration needs to performed with a closed system.

Emergence coughing is a challenging issue and a variety of medications have been proposed to prevent it. Administration of intravenous lidocaine (which is readily available) prior to tracheal extubation can effectively reduce emergence coughing (34). Also dexmedetomidine (0,5-1 μg/kg IV) is being put forward to prevent emergence coughing and appears to be effective (35).

Regional or general anesthesia

To diminish the number of aerosol generating procedures, the use of neuraxial anesthesia and peripheral nerve blocks is preferred in infected patients whenever possible, as stated by a Joint Statement of the American and European Societies of Regional Anesthesia and Pain Medicine (36, 37). Critical minds point to the risk of the coughing patient, but the odds of transmitting a respiratory infection to a HCW during tracheal intubation is 6.6 times compared to those who are not exposed to tracheal intubation (28). Patients should wear a surgical mask and if oxygen supplementation is

required, the oxygen mask can be put over or under the surgical mask.

Moreover, regional anesthesia has less impact on the patient's respiratory function, which is specifically important in symptomatic patients or patients with confirmed abnormalities on thoracic CT. For upper limb surgery the option with the least respiratory consequence should be chosen, such as an axillary block, or infraclavicular block. Normal precautions and contra-indications should be taken into account before performing the block. It is advisable to exclude thrombocytopenia in COVID-19 positive patients. The Obstetric Anesthetists' Association suggests outweighing risk-benefit in febrile patients (38), in truly septic patients neuraxial block is always contraindicated. Vigilance for hypotension during neuraxial block is recommended (36, 37).

Placing a nerve block should always be performed by the most experienced clinician, inside the dedicated OR, after taking all precautions on PPE. FFP2 masks are preferred over surgical masks (7, 11), although performing regional anesthesia is not considered an AGP conversion to general anesthesia (GA) is. All necessary medication should be prepared outside in advance, and the ultrasound machine should be adequately protected with a plastic cover and probe sheet. The advantage of perineural adjuncts should, as always, be balanced against the risks. No clear recommendations on this topic are present until now. Adequacy of the block should be tested thoroughly before proceeding to surgery, to avoid the need for sedation or unplanned conversion to GA. If the complexity of the surgery means a high probability the procedure cannot be entirely performed under regional anesthesia, it is better to start with GA anyway. Additional analgesic blocks during GA may be helpful in reducing PONV risk and opioid requirements and thus respiratory consequences postoperatively. Nevertheless, it is not recommended to reposition the patient for an additional block, as this imposes a risk of disconnection of the ETT (36).

Preoperative testing

In case of a positive patient presenting for surgery, local guidelines are usually clear. The surgery is performed in the dedicated OR and all staff is aware all available protective measures should be taken.

Confusion starts when other patients present for surgery. During the COVID-19 pandemic elective cases have been postponed in most institutions to create space on wards and the ICU, reduce resource demands and to allow relocation of OR staff to services where help is needed. However, clinicians have to decide whether it is justified to perform urgent cases. The American College of Surgeons presents an extensive list for guidance on triage decision making (39).

As the operative setting presents a high risk of contamination and transmission, ideally the viral status of all surgical patients should be known. Unfortunately the PCR laboratory capacity in many institutions cannot facilitate routine testing at this time. Moreover, PCR testing of SARS-CoV-2 on respiratory specimens (nasopharyngeal swab or sputum) has a significant number of false negative results of up to 29%, depending on time of testing since symptom onset and quality of the sampling (40, 41).

Institutional guidelines for preoperative PCR testing can be based on clinical presentation. The surgeon is responsible for taking a risk history before planning. A PCR test should at least be performed if the patient has a suspicious history (e.g. in case of COVID-19 fever, cough, sore throat, myalgia, chest tightness, anosmia, ageusia or living with a COVID-19 positive housemate) If the degree of urgency doesn't allow delay until PCR results are present, the patient should be treated as 'Patient Under Investigation' (PUI), and all measures should be taken as for the COVID-19 positive patient with the surgery taking place in the dedicated COVID-OR. Rapid antigen tests are available but are less sensitive than PCR. A negative antigen test should always be followed by a PCR. Thoracic CT or lung ultrasound may provide useful information, although findings are not specific and routine use for diagnosis is not recommended (42, 43). The high number of false negative PCR results has important implications on transmission risk and in case of clinical suspicion thoracic CT and a new PCR test after 24 to 48 hours should be performed, if possible on a lower respiratory tract specimen.

Considering the extent of contamination in society, the possibility of transmission through asymptomatic patients and the number of false negative PCR, ideally all AGP's, even if there is no clinical suspicion, should be considered as possibly contaminating (11, 36), although not performed in the dedicated OR. The Anesthesia Patient Safety Foundation recommends escalation of protection during all AGP (gown, FFP2 or FFP3 mask, goggles or face shield, double gloving). Consequently this poses a pressure on the already limited availability of PPE. For non-suspicious patients, treated in a non-

dedicated OR, it would be advisable to remove the gown after finishing AGP to prevent contaminating trays and cupboards. Besides that, the number of staff involved during AGP should be limited for every case and filters used to protect the anesthesia ventilator from contamination.

Conclusion

Respiratory pathogens, like SARS-CoV-2, are primarily transmitted through contact and droplet contamination, but prudent attitude implicates prevention of possible airborne transmission as well, mostly by AGP. Surgery on infected patients should be performed in a dedicated OR, and airflow contamination of surrounding rooms or corridors should be prevented. Careful OR management can limit number of involved personnel and isolate pathways from non-infected patients. The anesthesia ventilator should be protected with a mechanical HEPA breathing circuit filter on the Y-piece, and a second filter with high VFE on the expiratory limb is advisable. One of these should be HME during long procedures. Direction of gas sampling flow through the ventilator should be known and if possible scavenged. FFP2 respirator masks or equivalent should be worn at least during all AGP, as well as a long-sleeved impermeable gown of standardized quality, eye protection, gloves and a surgical hat. Intubation and extubation should be performed following a strict protocol and the number of persons involved should be limited. When possible, regional anesthesia is preferable. During a pandemic all patients should be regarded possibly infective, and local policies should include additional safety measures for all patients.

References

1. European Centre for Disease Prevention and Control. 2020. Guidance for wearing and removing personal protective equipment in healthcare settings for the care of patients with suspected or confirmed COVID-19. https://www.ecdc.europa.eu/en/publications-data/guidance-wearing-and-removingpersonal-protective-equipment-healthcare-settings (accessed 4th April 2020).
2. World Health Organization. 2020. Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected. Interim guidance. https://www.who.int/publications-detail/infection-prevention-and-control-duringhealth-care-when-novel-coronavirus-(ncov)-infection-is-suspected-20200125.(accessed 9th April 2020).
3. Centers of Disease Control and Prevention. 2020. Interim Infection Prevention and Control Recommendations for Patients with Suspected or Confirmed Coronavirus Disease 2019 (COVID-19) in Healthcare Settings. https://www.cdc.gov/coronavirus/2019-ncov/hcp/infection-controlrecommendations.html (accessed 7th April 2020).
4. Centers of Disease Control and Prevention. 2019. Guidelines for Environmental Infection Control in Heath-Care Facilities. https://www.cdc.gov/infectioncontrol/guidelines/environmental/index.html (accessed 7th April 2020).
5. Judson S.D. and Munster V.J. 2019. Nosocomial Transmission of Emerging Viruses via Aerosol-Generating Medical Procedures. Viruses. 11(10).
6. European Centre of Disease Prevention and Control. 2014. Safe use of personal protective equipment in the treatment of infectious diseases of high consequence. https://www.ecdc.europa.eu/en/publications-data/safe-use-personal-protectiveequipment-treatment-infectious-diseases-high (accessed 4th April 2020).
7. Setti L., Passarini F., De Gennaro G., Barbieri P., Perrone M.G. and Borelli M., et al. 2020. Airborne Transmission Route of COVID-19: Why 2 Meters/6 Feet of Inter-Personal Distance Could Not Be Enough. Int J Environ Res Public Health. 17(8):2932.
8. Bahl P., Doolan C., de Silva C., Chughtai A.A., Bourouiba L. and MacIntyre C.R. 2020. Airborne or Droplet Precautions for Health Workers Treating COVID-19? J Infect Dis. Epub ahead of print 16th April. doi: 10.1093/infdis/jiaa189
9. Cook T.M. 2020. Personal protective equipment during the coronavirus disease (COVID) 19 pandemic - a narrative review. Anesthesia. Epub ahead of print 4th April. https://doi.org/10.1111/anae.15071
10. Dexter F., Parra M.C., Brown J. and Loftus R.W. 2020. Perioperative COVID-19 Defense: An Evidence-Based Approach for Optimization of Infection Control and Operating Room Management. Anesth Analg. Epub ahead of print 26th March.
11. Zucco L., Levy N., Ketchandji D., Aziz M. and Ramachandran S.K. 2020. Perioperative Considerations for the 2019 Novel Coronavirus (COVID-19). https://www.apsf.org/news-updates/perioperative-considerations-for-the-2019-novel-coronavirus-covid-19/ (accessed 11th April 2020).
12. Pryor A. 2020. SAGES and EAES Recommendations regarding surgical response to COVID-19 crisis. https://www.sages.org/recommendations-surgical-responsecovid-19/ (accessed 1st April 2020).
13. Kwak H.D., Kim S.H., Seo Y.S. and Song K.J. 2016. Detecting hepatitis B virus in surgical smoke emitted during laparoscopic surgery. Occup Environ Med. 73(12):857-63.
14. Zhai Z. and Osborne A.L. 2013. Simulation-based feasibility study of improved air conditioning systems for hospital operating room. Frontiers of Architectural Research. 2(4):468-75.
15. Sadrizadeh J.S. and Holmberg S. 2014. Surgical clothing systems in laminar airflow operating room: a numerical assessment. Journal of Infection and Public Health. 7(6):508-16.
16. Xiangdong C., Yanhong L., Yahong G., Xiangyang G., Mingzhang Z. and Jun L., et al. 2020. Perioperative Management of Patients Infected with the Novel Coronavirus : Recommendation from the Joint Task Force of the Chinese Society of Anesthesiology and the Chinese Association of Anesthesiologists. Anesthesiology. 132:1307-16.
17. Zhang B., Li. L., Yao X., Gong Y., Zhang Y. and Yang H., et al. 2020. Analysis of Air Purification Methods in Operating Rooms of Chinese Hospitals. Biomed Res Int. 2020 : ID 8278943.

18. van Doremalen N., Bushmaker T., Morris D.H., Holbrook M.G., Gamble A. and Williamson B.N., et al. 2020. Aerosol and Surface Stability of SARS-CoV-2 Compared with SARS-CoV- 1. N Engl J Med. 382(16):1564-67.
19. European Centre for Disease Prevention and Control. 2020. Infection prevention and control and preparedness for COVID-19 in healthcare settings - second update. https://www.ecdc.europa.eu/en/publications-data/infection-prevention-and-controland-preparedness-covid-19-healthcare-settings (accessed 4th April 2020).
20. Feldman J., Loeb R. and Philip J. 2020. Anesthesia Patient Safety Foundation. FAQ on Anesthesia Machine Use, Protection and Decontamination during the COVID-19 Pandemic. https://www.apsf.org/faq-on-anesthesia-machine-use-protection-and-decontaminationduring-the-covid-19-pandemic/ (accessed 10th April 2020).
21. Wilkes A.R. 2011. Heat and moisture exchangers and breathing system filters : their use in anaesthesia and intensive care. Part 1 – history, principles and efficiency. Anaesthesia. 66(1):31-9.
22. Agency. MaHPR. 2004. Breathing System Filters. An Assessment of 104 Different Breathing System Filters. https://www.psnetwork.org/wpcontent/uploads/2018/01/An-assessment-of-104-breathing-system-filters-MHRAEvaluation-04005-2004-.pdf (accessed 10th April 2020).
23. Kramer A., Kranabetter R., Rathgeber J., Züchner K., Assadian O. and Daeschlein G., et al. 2010. Infection prevention during anaesthesia ventilation by the use of breathing system filters (BSF): joint recommendation by German Society of Hospital Hygiene (DGKH) and German Society for Anaesthesiology and Intensive Care (DGAI). GMS Krankenhhyg Interdiszip. 5(2).
24. Hartmann D., Jung M., Neubert T.R., Susin C., Nonnenmacher C. and Mutters R.. 2008. Microbiological risk of anaesthetic breathing circuits after extended use. Acta Anaesthesiol Scand. 52(3):432-6.
25. European Centre for Disease Prevention and Control. 2020. Personal Protective Equipment (PPE) needs in heathcare settings for the care of patients with supected or confirmed novel coronavirus (2019-nCoV). https://www.ecdc.europa.eu/en/publicationsdata/personal-protective-equipment-ppe-needs-healthcare-settings-care-patients (accessed 8th April 2020).
26. Wely E.V. 2017. Current global standards for chemical protective clothing: how to choose the right protection for the right job? Ind Health. 55(6):485-99.
27. Laer F.V.. 2019. Graad van bescherming van beschermingspakken tegen biologische agentia. http://www.nosoinfo.be/nosoinfos/graad-van-bescherming-van-beschermingspakken-tegen-biologische-agentia/?lang=nl (accessed 9th april).
28. Tran K., Cimon K., Severn M., Pessoa-Silva C.L., Conly J. 2012. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: A systematic review. PLoS One. 7(4):e35797.
29. Baig M.A. 2020. The COVID-19 Intubation and Ventilation Pathway (CiVP) ; a Commentary. Arch Acad Emerg Med. 8(1):e37.
30. Orser B.A. 2020. Recommendations for Endotracheal Intubation of COVID-19 Patients. Anesth Analg. 2020. 130(5):1109-10.
31. American Society of Anesthesiologists Task Force on Management of Difficult Airway. 2013. Practice Guidelines for Management of the Difficult Airway: An Updated Report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. Anesthesiology. 118:251-70.
32. Li J., Fink J.B., Ehrmann S. 2020. High-flow Nasal Cannula for COVID-19 Patients: Low Risk of Bio-aerosol Dispersion. Eur Respir J. 55(5):2000892.
33. Pandey C.K., Raza M., Ranjan R., Singhal V., Kumar M. and Lakra A., et al. 2005. Intravenous lidocaine 0.5 mg.kg-1 effectively suppresses fentanyl-induced cough. Can J Anaesth. 52(2):172-5.
34. Yang S.S., Wang N.N., Postonogova T., Yang G.J., McGillion M. and Beique F., et al. 2020. Intravenous lidocaine to prevent postoperative airway complications in adults: a systematic review and meta-analysis. Br J Anaesth. 124(3):314-23.
35. Tung A., Fergusson N.A., Ng N., Hu V., Dormuth C. and Griesdale D.E.G. 2020. Medications to reduce emergence coughing after general anaesthesia with tracheal intubation: a systematic review and network meta-analysis. Br J Anaesth. Epub ahead of print 22nd February. doi: 10.1016/j.bja.2019.12.041
36. Uppal V., Sondekoppam R.V., Lobo C.A., Kolli S. and Kalagara H.K.P. 2020. Practice Recommendations on Neuraxial Anesthesia and Peripheral Nerve Blocks during the COVID-19 Pandemic A Joint Statement by the American Society of Regional Anesthesia and Pain Medicine (ASRA) and European Society of Regional Anesthesia and Pain Therapy (ESRA) https://www.asra.com/page/2905/practice-recommendations-on-neuraxial-anesthesia-and-peripheral-nerve-blocks-dur (accessed 10th April 2020)
37. Lie S.A., Wong S.W., Wong L.T., Wong T.G.L., and Chong S.Y. 2020. Practical considerations for performing regional anesthesia: lessons learned from the COVID-19 pandemic. Can J Anaesth. Epub ahead of print 24th March. doi: 10.1007/s12630-020-01637-0
38. Kimber Craig S., Moss S., McTavish A. and Susnerwala I. 2020. Standard Operating Procedure for the Obstetric and Theatre Management of Women with Suspected or Confirmed COVID-19 on Central Delivery Suite https://www.oaa-anaes.ac.uk/assets/_managed/cms/files/COVID%20obs%20anaesthesia%20SOP%20obstetrics%20additions%20-%20Kimber%20Craig-%20Bolton.pdf (accessed 13th April 2020).
39. Surgeons ACo. 2020. COVID-19: Elective Case Triage Guidelines for Surgical Care. https://www.facs.org/covid-19/clinical-guidance/elective-case (accessed 10th April 2020).
40. Li Y., Yao L., Li J., Chen L., Song Y., Cai Z. and Yang C. 2020. Stability Issues of RT-PCR Testing of SARS-CoV-2 for Hospitalized Patient Clinically Diagnosed with COVID-19. J Med Virol. Epub ahead of print 5th April. doi: 10.1002/jmv.25786
41. Arevalo-Rodriguez I., Buitrago-Garcia D., Simancas-Racines D., Zambrano-Achig P., del Campo R. and Ciapponi A., et al. 2020. False-negative Results of Initial RT-PCR Assays for COVID-19: A Systematic Review. Preprint on medrxiv.org 21th April. doi: 10.1101/2020.04.16.20066787
42. Hope M.D., Raptis C.A., Shah A, Hammer M.M. and Henry T.S. 2020. A role for CT in COVID-19? What data really tell us so far. Lancet. 395(10231):1189-90.
43. Radiology ACo. 2020. ACR Recommendations for the use of Chest Radiography and Computed Tomography (CT) for Suspected COVID-19 Infection. https://www.acr.org/Advocacy-and-Economics/ACR-Position-Statements/Recommendations-for-Chest-Radiography-and-CT-for-Suspected-COVID19-Infection (accessed 10th April 2020).

NRFit®

For More Patient Safety

New ISO standard
in Regional Anaesthesia

REGIONAL ANAESTHESIA
& PAIN MANAGEMENT

*NRFit is a registered trademark of GEDSA used with their permission.

PAJUNK®
Trust Tradition. Experience Innovation.

- → Clear labeling on products and packaging
- → Work process remains the same
- → Faulty connections nearly eliminated

LUER

NRFit®

PAJUNK® NRFit
Products

LEARN MORE ABOUT ***NRFIT***
info@pajunk-medipro.com

(Acta Anaesth. Belg., 2020, 71, 123-130)

Reliability of a spot check non-invasive hemoglobin monitoring (SpHb) of the Masimo RAD-67™ and the HemoCue® for anemia screening

W. Baulig (*), U. Eichenberger (**), O.M. Theusinger (***)

Abstract : *Background :* To test the reliability of the spot check Masimo Rad-67 (Masimo Corp., Irvine, CA, USA) as part of a preoperative anemia screening, hemoglobin measurements were compared to those of the HemoCue® Hb 201+ System (HemoCue AB, Ängelholm, Sweden) and the standard laboratory measurement.

Methods : During preoperative evaluation of patients scheduled for elective orthopedic surgery hemoglobin concentration was simultaneously determined by standard laboratory analysis (Hb_{Lab}), the HemoCue® Hb 201+ System ($Hb_{Hemocue}$) and by Pulse Co-Oximetry using the Masimo Rad-67 (SpHb) with the rainbow® DCI®-mini Sensor (Masimo Corp., Irvine, CA, USA). Linear correlation, agreement (Bland-Altman analysis), sensitivity/specificity and positive/negative prediction values (PPV/NPV) for anemic hemoglobin values were determined. P-values less than 0.05 were considered statistically significant.

Results : 303 patients were analyzed. Twenty-one patients (12 male and 9 female) had mild or moderate anemia, detected by Hb_{Lab}. In 20 patients, the $Hb_{Hemocue}$, and in 34 patients, the SpHb detected anemia. Linear correlation and mean bias (limits of agreement, LOA) for $Hb_{Hemocue}$ and Hb_{Lab} were r = 0.969 and -1.08 (+6.44/-8.60) g/L, and for SpHb and Hb_{Lab} r = 0.61 and +1.76 (+26.92/-23.4) g/L. Sensitivity/specificity of the $Hb_{Hemocue}$ to detect anemia in all, male and female patients were 85.0/99.3%, 75.0/100/% and 88.9/98.9/% with a PPV/NPV of 89.5/98.9%, 100/98.0% and 80.0/99.3%, respectively. Sensitivity/specificity of SpHb to detect anemia for all, male and female patients were 71.4%, 93.3%, 75.0/95.2/% and 66.7/91.1%, with a PPV/NPV for all, male and female patients of 44.1/97.8%, 56.3/97.9% and 33.3/97.7%, respectively.

Conclusions : $Hb_{Hemocue}$ and Hb_{Lab} show a strong linear correlation and a good agreement, while linear correlation of SpHb and Hb_{Lab} is moderate and agreement poor. For both devices, anemia detection is moderate, but the positive prediction value for anemia is much better with the $Hb_{Hemocue}$. Both devices reliably detected non-anemic patients.

Glossary : CO = carbon monoxide ; PPV = positive predicted value ; NPV = negative predicted value ; Hb_{Lab} = hemoglobin determined by the laboratory ; $Hb_{Hemocue}$ = hemoglobin determined by the HemoCue device ; SpHb = hemoglobin determined by the Masimo-RAD67 device ; LOA = limits of agreement ; LOS = length of stay ; POC = point of care ; SpO_2 = arterial hemoglobin ; PR = pulse rate ; PI = perfusion index ; PVI = plethysmography variability index ; SpCO = carboxyhemoglobin ; SpMet = methemoglobin ; LED = Light Emitting Diodes ; HiCN = hemiglobincyanide ; SLS = Sodium Lauryl Sulphate ; BMI = body mass index ; BT = body temperature ; WHO = World Health Organization ; IQR = interquartile range ; MAP = mean arterial pressure ; HF = heart frequency ; SD = standard deviation

Key point Summary :

– *Question :* Is Hb measurement of the Masimo Rad-67 and of the HemoCue reliable?

– *Findings :* Non-anemic patients are reliably detected with the Masimo Rad-67. Of the 303 patients examined, Hb_{Lab} detected twenty-one patients (12 male and 9 female) with mild or moderate anemia. The Hbh_{emocue} showed anemia in 20 patients, while the SpHb identified 34 patients as anemic. $Hb_{Hemocue}$ and Hb_{Lab} showed a strong linear correlation and a good agreement, while linear correlation of SpHb and Hb_{Lab} was moderate and agreement poor. For both devices, anemia detection is moderate, but the positive prediction value for anemia is much better with the $Hb_{Hemocue}$. Both devices reliably detected non-anemic patients.

Werner Baulig, MD ; Urs Eichenberger, MD ; Oliver M. Theusinger, MD

(*) Department of Anesthesiology and Intensive Care Medicine, Klinik Im Park, Zurich, Switzerland

(**) Department of Anesthesiology, University Hospital Balgrist and University of Zurich, Zurich, Switzerland

(***) During the Study Department of Anesthesiology, University Hospital Balgrist and University of Zurich, Zurich, Switzerland, actually University of Zurich, Zurich, Switzerland

Corresponding author : Oliver M. Theusinger, MD, University of Zurich, CH – 8001 Zurich, Switzerland - Phone : + 41 79 659 50 05

Email : Oliver@theusinger.de

Paper submitted on May 15, 2020 and accepted on August 25, 2020

Conflict of interest : Oliver M. Theusinger has received honoraria or travel support for consulting or lecturing from the following companies : CSL Behring Schweiz, Zurich, Switzerland, Vifor SA, Villars-sur-Glâne, Switzerland, Roche Pharma (Schweiz) AG, Reinach, Switzerland, Pentapharm AG, München, Germany, TEM International GmbH, München, Germany, Octapharma AG Lachen, Switzerland, Instrumentation Laboratory, Bedford, MA, USA. Urs Eichenberger has no conflict of interest. Werner Baulig has no conflict of interest.

– *Meaning :* With both devices, non-anemic patients are reliably recognized, while anemia detection is moderate. However, the prediction for the presence of anemia is much better with the $Hb_{hemocue}$.

Key words : Anemia ; orthopedic surgery ; non-invasive hemoglobin measurement ; Masimo ; RAD-67™ ; HemoCue®.

Introduction

Preoperative evaluation and optimization of the patients' red blood cells have been shown to be beneficial for outcomes after major surgery (1). In patients undergoing elective orthopedic surgery, preoperative anemia, most commonly attributed to iron deficiency, is present in about 19.4 to 35% and associated with increased hospital length of stay (LOS), morbidity and mortality (2,3). Recently, Froessler et al. showed that perioperative administration of ferric carboxymaltose in preoperative anemia resulted in a significant reduction of patient-related hospital costs, mainly based on reduced blood transfusions and LOS (4).

Screening for anemia in elective orthopedic surgery during a first preoperative evaluation is important to create the best possible entry conditions for the patient. In our center, preoperative evaluation is usually done 4 to 6 weeks prior to surgery with hemoglobin concentration being measured using a Point of care (POC) device HemoCue® Hb 201$^+$ Analyzer (HemoCue AB, Ängelholm, Sweden). In case of preoperative anemia, the general practitioner is encouraged to carry out further diagnostics and initiate preoperative anemia therapy. Most recently, the Rad-67™ Pulse CO-Oximeter® (Masimo Corp., Irvine, CA, USA) with the rainbow® DCI®-mini Sensor (Masimo Corp., Irvine, CA, USA) has become available, providing hemoglobin concentration by non-invasive spot-check measurements using the multi-wavelength pulse CO-oximetry technology.

The aim of this study was to investigate the feasibility and reliability of the spot check Rad-67™ Pulse CO-Oximeter® (Rad-67) and the HemoCue® Hb 20$^+$ Analyzer in measuring hemoglobin concentrations during the early preoperative evaluation of elective orthopedic surgery patients. For this, we compared the obtained results of with those measured using a standard laboratory analyzer (XN 9000 Hematology analyzer, Sysmex (Sysmex Corporation, Kobe, Japan).

Materials and Methods

This study was performed after obtaining approval from the local ethics committee (Kantonale Ethikkommission, Kanton Zürich, Switzerland, BASEC-Nr :2017-01361/ cliniclatrials.gov NCT 03328780). After written informed consent had been obtained from the patient, demographic data were collected and measurements were performed. Data were collected in the University Hospital Balgrist in Zurich, Switzerland, from 11/2017 till 02/2018.

The spot check Rad-67™ Pulse CO-Oximeter® (Rad-67) is a non-invasive device monitoring the functional oxygen saturation of arterial hemoglobin (SpO_2), pulse rate (PR), perfusion index (PI), plethysmography variability index (PVI), and allowing a spot check monitoring of total hemoglobin (SpHb), carboxyhemoglobin (SpCO) and methemoglobin (SpMet). SpO_2 and PR measurements are possible even during motion and at phases of weak circulation. After the sensor is initialized, the signal stabilized and sufficient blood perfusion detected, the one-time SpHb value is displayed for 5 minutes or until the sensor is removed. With the Signal Extraction Technology® (SET®), the impact of motion of the arterial or venous blood during changes in the patient's position is removed by adaptive filters. The Rad-67™ uses the rainbow® DCI®-mini Sensor with different Light Emitting Diodes (LED) which guide light to a photodiode (photodetector). The signal data is determined by passing different visible light and infrared light of wavelengths between 500 and 1400nm through the capillary bed at the tip of the patient's finger and measuring the changes in light absorption during the pulsatile blood cycle. The photodetector receives the light, converts it to an electrical signal, and transmits the signal to the Rad-67™ device. SpHb measurement relies on a calibration equation of multiple wavelengths which quantifies the percentage of total blood hemoglobin.

The PI (range 0 to 20) is the ratio of pulsatile blood flow to non-pulsatile or static blood in the peripheral tissue. PI < 1 is associated with incorrect measurement results. The Rad-67™ displays the calculated data of methemoglobin as a percentage for SpMet and values > 1% in non-smoking adults are defined as pathological.

The HemoCue® Hb 201$^+$ analyzer (HemoCue) is a POC device providing quantitative determination of the total amount of hemoglobin ($Hb_{Hemocue}$) in whole blood. Capillary, venous or arterial whole blood may be used in specially designed microcuvettes. The system is factory

calibrated against the hemiglobincyanide (HiCN) method. Sodium deoxycholate hemolyzes the erythrocytes and hemoglobin is released. Using the modified Vanzetti's azide technique, sodium nitrite converts hemoglobin to methemoglobin, which, together with sodium azide, results in azide methemoglobin. The latter has almost the same absorbance spectrum as that of HiCN. Absorbance is measured at two wavelengths (570 and 880nm) in order to compensate for turbidity in the sample. The reliable measuring range of hemoglobin is 0 – 256 g/L (0 – 15.9mmol/L). Results above 256g/L (> 15.9mmol/L) are displayed as HHH. The analyzer is suited for both static and mobile use and stores test results, date and time for up to 600 measurements.

The XN 9000 Hematology Analyzer (XN 9000) for laboratories determines the total hemoglobin concentration (Hb_{Lab}) by the cyanide-free Sodium Lauryl Sulphate (SLS) method, the reliability of which has been demonstrated against the HiCN-Method in various investigations (5-8). SLS is a surfactant which both hemolyzes erythrocytes and rapidly forms a complex with the released hemoglobin. The product SLS-MetHb is stable for few hours and has a characteristic optical spectrum with maximum absorbance at 555 nm. Monochromatic light with a wavelength of 555 nm sent by the LED is absorbed by the SLS-MetHb complex. The extinction is measured by a photo sensor and is inversely proportional to the hemoglobin concentration of the sample, according to the Beer-Lambert's law. Turbidity of the sample caused by lipemia or leukocytosis is minimized due to the effect of the SLS reagent.

Upon arrival in the consulting room, the patient took place on a deckchair. According to the manufacturer's recommendation, the rainbow® DCI®-mini Sensor was attached to the finger as identified by the provided finger sizer of the dominant hand for transcutaneous measuring of SpHb and SpMet. The Rad-67 was calibrated for venous measurement of SpHb because blood samples for measuring Hb_{Lab} were taken from a venous vessel. After a five minutes waiting period, two blood samples were drawn from the cephalic vein of the opposite arm and the SpO_2, PR, PI, SpHb and SpMet values on the display of the Rad-67 were documented. The EDTA blood sample was sent to the central laboratory for analyzing Hb_{Lab}. One milliliter of venous blood was drawn in a blood gas analysis syringe (SafePICO aspirator, Radiometer Medical, Bronshoj, Denmark, containing 80 IU heparin) and $Hb_{Hemocue}$ was analyzed. In addition, gender (sex), age, body weight, height, body mass index (BMI), non-invasive blood pressure (systolic, diastolic, mean arterial pressure) and body temperature (BT) were registered. Anemia was defined as hemoglobin (Hb) levels < 120 g/L in women and < 130 g/L in men, according to the World Health Organization (WHO). Anemia was defined as mild, moderate or severe in women/men (15years of age and above) if Hb levels were 110-119/110-129g/L, 80-109/80-109 g/L and < 80/80 g/l, respectively (9).

Statistical Analyses :

Data were collected using Microsoft® Excel (Microsoft Office 2010, Microsoft Corporation Redmond, WA, US) and analyzed using IBM® SPSS® Statistics version 25 (IBM Corp, Armonk, NY, USA). The Kolmogorov-Smirnov-Test was used to test continuous variables on normality. Continuous variables of all patients were summarized as mean ± standard deviation (SD) or as median [IQR] according to the distribution of the data. Pearson Correlation Coefficient was used to test the linear relationship between Hb_{Lab} and $Hb_{Hemocue}$, and Hb_{Lab} and SpHb. For determination of the agreement between the different methods, Bland-Altman analysis was applied to assess mean bias and limits of agreement (LOA) of Hb_{Lab} with $Hb_{Hemocue}$ and SpHb (10). LOA is defined as (mean bias ± 2SD). To quantify the test performance, sensitivity / specificity and positive predictive value (PPV) / negative predictive value (NPV) of $Hb_{Hemocue}$ and SpHb were determined. Stepwise multiple regression analysis was used to estimate the impact of independent factors on the $Hb_{Hemocoue}$ and SpHb. P-values less than 0.05 were considered statistically significant.

Results

In total, 307 patients were investigated. Four patients had to be excluded from analysis because of a PI < 1. Demographic and physiologic data of the 303 remaining (157 male and 146 female) patients are presented in table 1. In 21 (7%) patients (12 male and 9 female), Hb_{Lab} detected anemia. Anemic patients were significantly older (p = 0.021) and the diastolic blood pressure was lower (p = 0.021) when compared to patients without anemia. Mild anemia was found in 11 male and 6 female patients. One male and three female patients had moderate anemia. In 64 (21%) patients (33 male and 31 female), MetHb > 1 was found. The median (IQR) PI of the Rad-67 was 5.3 (3.1; 8.1) with significant higher PI-values in males compared to females (Table 1).

Table I.

Demographic and physiologic data of all, female and male patients. Data are presented as mean ± SD or median [IQR] ; p-values less than 0.05 are considered statistically significant.

	All (n = 303)	Male (n = 157)	Female (n = 146)	p-value
Age, yr	53.3 [37.6; 67.6]	51.1 [38.6; 66.2]	55.8 [34.4; 69.0]	n.s.
Heigh, cm	170.1±10.4	176.3±8.4	163.3±7.9	< 0.001
Weight, kg	78.0 [67.5; 90.0]	84.0 [75.2; 98.5]	70.0 [60.4; 80.4]	< 0.001
BMI, kg/m^2	27.1 [23.7; 30.7]	27.5 [24.4; 31.2]	26.3 [22.5; 30.7]	n.s.
HF, bpm	75 [68; 84]	75 [67; 84]	76 [69; 83]	n.s.
BP_{syst}, mmHg	136.6±17.8	138.7±15.8	134.5±19.6	= 0.041
BP_{diast}, mmHg	82.5±11.9	84.8±11.8	79.9±11.4	< 0.001
MAP, mmHg	100.5±12.4	102.8±11.5	98.1±12.9	= 0.001
SpO_2, %	97 [96; 98]	97 [96; 98]	97 [96; 98]	n.s.
BT, °C	36.8 [36.5; 37.0]	36.6 [36.3; 36.9]	36.9 [36.6; 37.2]	n.s.
Hb_{Lab}, g/L	142.4±14.6	149.6±14.0	134.6±10.8	< 0.001
$Hb_{Hemocue}$, g/L	143.5±15.1	150.9±14.4	135.5±11.3	< 0.001
SpHb, g/L	140.6±13.7	145.4±12.5	135.5±13.1	< 0.001
PI	5.3 [3.1; 8.1]	6.3 [3.6; 8.8]	5.3 [2.4; 6.9]	> 0.001
MetHb	0.8 [0.5; 1.1]	0.8 [0.5; 1.1]	0.8 [0.5; 1.1]	n.s.

Abbreviations: BMI, body mass index; BP_{syst}, systolic arterial pressure; BP_{diast}, diastolic arterial blood pressure; MAP, mean arterial pressure; SpO_2, oxygen saturation measured by pulse oximetry; BT, body temperature; Hb_{Lab}, Hb measured by the XN 9000 Hematology Analyzer; $Hb_{Hemocue}$, Hb concentration measured by the Hemocue device; SpHb, Hb concentration measured by the RAD-67 device; PI, pulsation index measured by the Rad 67™ n.s., not significant.

Table II

Linear correlation and agreement of of Hb_{Lab} and $Hb_{Hemocue}$ in all, male and female patients, patients with and without anemia

	r	CI95	r^2	p-value	Bias (g/L)	SD (g/L)	LOA (g/L)
All	0.969	0.973; 1.031	0.938	< 0.001	-1.08	±3.76	(+6.44/-8.60)
Male	0.963	0.948; 1.037	0.927	< 0.001	-1.29	±3.90	(+6.52/-9.09)
Female	0.948	0.937; 1.046	0.899	< 0.001	-0.86	±3.60	(+6.35/-8.06)
$All_{no\ anemia}$	0.958	0.968; 1.038	0.918	< 0.001	-1.05	±3.78	(+6.51/-8.61)
$Male_{>130}$	0.936	0.923; 1.045	0.876	< 0.001	-1.25	±3.89	(+6.53/-9.03)
$Female_{>120}$	0.922	0.921; 1.063	0.850	< 0.001	-0.83	±3.66	(+6.49/8.15)
All_{anemia}	0.957	0.985; 1.319	0.917	< 0.001	-1.52	±3.53	(+5.54/-8.58)
$Male_{<130}$	0.953	0.958; 1.513	0.908	< 0.001	-1.75	±4.20	(+6.65/-10.15)
$Female_{<120}$	0.957	0.766; 1.333	0.916	< 0.001	-1.22	±2.59	(+3.95/-6.39)

Abbreviations: Hb_{Labs}, photometrically measured Hb; $Hb_{Hemocue}$, Hemoglobin concentration measurement by the Hemocue device; SpMet, Methemoglobin measured with the Rad 67; $All_{no\ anemia}$, all patients without anemia; $Male_{>130}$, Male with Hb_{Labs} > 130g/L; $Female_{>120}$, female with Hb_{Labs} > 120g/L; All_{anemia}, all patients with anemia; $Male_{<130}$, males with Hb_{Labs} < 130g/L; $Female_{<120}$, female with Hb_{Labs} < 120g/L; bias, mean of the differences between Hb_{Labs} and $Hb_{Hemocue}$; LOA, limits of agreement (mean bias ±2 SD).

Comparison between the Hb_{Lab} and $Hb_{Hemocue}$

In all patients, Hb_{Lab} and $Hb_{Hemocue}$ showed a strong linear correlation (r = 0.969) and a mean bias (LOA) of -1.08 (+6.44 / - 8.60) g/L (Table II, Fig. 1). No significant changes of the linear correlation and in the agreement were found in male and female patients or in patients with or without anemia (Table II, Fig 1). Stepwise multi-regression analysis showed a significant impact of HF (p = 0.036), MAP (p > 0.001), age (p < 0.001) and BT (p = 0.001) on the $Hb_{Hemocue}$. Sensitivity/specificity of the $Hb_{Hemocue}$ to detect anemia for all, male and female patients was 85.0/99.3%, 75.0/100% and 88.9/98.9% with a PPV/NPV for all, male and female patients of 89.5/98.9%, 100/98.0% and 80.0/99.3%, respectively (Table IV). $Hb_{Hemocue}$ detected anemic values in 20 patients (9 male and 11 female).

Comparison between the Hb_{Lab} and SpHb

In all patients, Hb_{Lab} and SpHb showed a moderate linear correlation (r = 0.607) and a mean bias (LOA) of +1.76 (+26.92 / - 23.40) g/L (Table III, Fig 2). In the subgroup of non-anemic males, the mean bias (LOA) of Hb_{Lab} and SpHb was +5.32 (+29.99/-19.35) g/L, while in anemic males and females a mean bias (LOA) of -8.83 (+9.86/27.52)

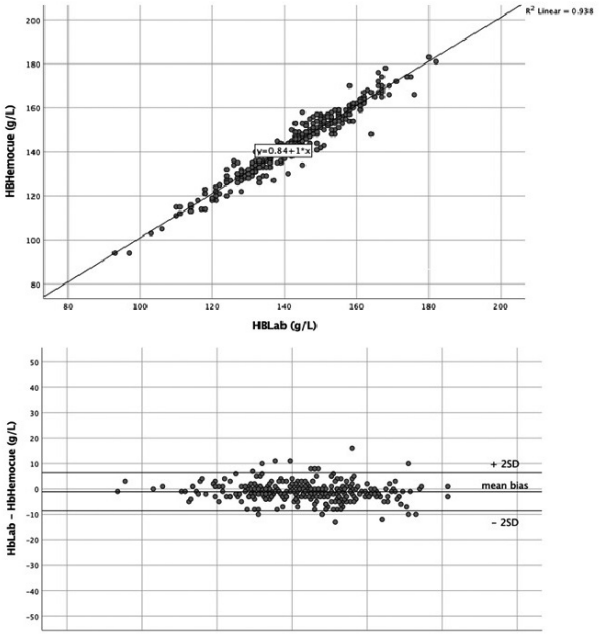

Fig.1. —A, Correlation of the Masimo-RAD67 hemoglobin measurements versus hemoglobin determination with HemoCue. B, Bland-Altmann plot for the hemoglobin determination with the Masimo-RAD67 and the determination with HemoCue.

surgery, we found anemic values in only 7% of the included patients, which might be explained by a high proportion of younger patients (< 65 years) (11). In the present study, $Hb_{Hemocue}$ showed a strong linear correlation and a good agreement with Hb_{Lab} in all patients, while linear correlation of SpHb with Hb_{Lab} was only moderate and the agreement poor. Our results are in accordance with those of comparative studies with other Pulse CO-Oximeter devices. In adult emergency department patients, Knutson et al. reported limits of agreement for laboratory hemoglobin and SpHb measured with the Radical-7 Pulse CO-Oximeter of -47/+38g/l which was beyond the clinically relevant standard of equivalency (12). Similar results were found by Gayat et al. who compared laboratory hemoglobin concentration values with non-invasive detected hemoglobin of the Pronto-7 and the Orsense NMB-200 device in emergency room patients (13). Interestingly, while mean bias and agreement of Hb_{Lab} and $Hb_{Hemocue}$ was not different in the subgroup analysis of our study, mean bias of Hb_{Lab} and SpHb

Table III

Linear correlation and agreement of Hb_{Lab} and SpHb in all, male and female patients, patients with and without anemia

	r	CI95	r^2	p-value	Bias (g/L)	SD (g/L)	LOA (g/L)
All	0.607	0.483; 0.652	0.368	< 0.001	+1.76	±12.58	(+26.92/-23.40)
Male	0.547	0.370; 0.607	0.300	< 0.001	+4.24	±12.68	(+29.59/-21.12)
Female	0.513	0.449; 0.791	0.263	< 0.001	-0.90	±11.96	(+23.01/-24.82)
$All_{no\ anemia}$	0.528	0.441; 0.648	0.278	< 0.001	+2.54	±12.45	(+27.45/-22.37)
$Male_{>130}$	0.369	0.232; 0.563	0.136	< 0.001	+5.32	±12.34	(+29.99/-19.35)
$Female_{>120}$	0.418	0.376; 0.818	0.174	< 0.001	-0.40	±11.93	(+23.46/-24.26)
All_{anemia}	0.491	0.071; 0.900	0.241	= 0.024	-8.71	±9.34	(+9.63 /-27.29)
$Male_{<130}$	0.469	-0.146; 1.041	0.220	= 0.146	-8.83	±9.23	(+9.86/-27.518)
$Female_{<120}$	0.240	-0.644; 1.137	0.058	= 0.534	-8.56	±10.05	(+11.54/-28.66)

Abbreviations: Hb_{Labs}, photometrically measured Hb; SpHb, Hemoglobin concentration measurement by the Rad 67; SpMet, Methemoglobin measured with the Rad 67; $All_{no\ anemia}$, all patients without anemia; $Male_{>130}$, Male with Hb_{Labs} > 130g/L; $Female_{>120}$, female with Hb_{Labs} > 120g/L; All_{anemia}, all patients with anemia; $Male_{<130}$, males with Hb_{Labs} < 130g/L; $Female_{<120}$, female with Hb_{Labs} < 120g/L; bias, mean of the differences between Hb_{Labs} and SpHb; LOA, limits of agreement (mean bias ±2 SD).

g/L and -8.56 (+11.54/-28.66) g/L was found, respectively (Table III). Stepwise multi-regression analysis showed a significant effect of HF ($p = 0.01$), MAP ($p < 0.001$), PI ($p < 0.001$), age ($p > 0.001$) and MetHb ($p = 0.001$) on SpHb. Sensitivity/specificity of SpHb to detect anemia for all, male and female patients was 71.4/93.3%, 75.0/95.2% and 66.7/91.1%, with a PPV/NPV for all, male and female patients of 44.1/97.8%, 56.3/97.8% and 33.3/97.7%, respectively (Table IV). SpHb detected anemic values in 34 patients (16 male and 18 females).

Discussion

The main results of this first investigation of the Rad-67 in comparison with the HemoCue are : i) $Hb_{Hemocue}$ showed a strong linear correlation and good agreement with Hb_{Lab}, while linear correlation of SpHb and Hb_{Lab} was moderate and agreement poor ; ii) for both devices, anemia detection was moderate, but the positive prediction value for anemia was much better with the $Hb_{Hemocue}$, iii) both devices reliably detected non-anemic patients.

In contrast to the expected prevalence of anemia in patients scheduled for elective orthopedic

Table IV

Sensitivity/specificity and PPV/NPV for $Hb_{Hemocue}$ and SpHb to detect anemia.
True normal was defined as Hb_{Lab} > 130g/L for men and Hb_{Lab} > 120g/l for female.

	all			Male			Female		
	Hb_{Lab}	$Hb_{Hemocue}$	SpHb	Hb_{Lab}	$Hb_{Hemocue}$	SpHb	Hb_{Lab}	$Hb_{Hemocue}$	SpHb
		n (%)	n (%)		n (%)	n (%)		n (%)	n (%)
All patients	n = 303			n = 157			n = 146		
True normal	282 (93.1)	281	263	145	145	138	137	135	125
True anemia	21 (6.9)	17	15	12	9	9	9	8	6
False normal		3	6		3	3		1	3
False anemia		2	19		0	7		2	12
Sensitivity		(85.0)	(71.4)		(75)	(75)		(88.9)	(66.7)
Specificity		(99.3)	(93.3)		(100)	(95.2)		(98.9)	(91.1)
PPV		(89.5)	(44.1)		(100)	(56.3)		(80.0)	(33.3)
NPV		(98.9)	(97.8)		(98.0)	(97.9)		(99.3)	(97.7)

Abbreviations: HbLab, photometrically measured Hemoglobin concentration; $Hb_{Hemocue}$, Hemoglobin concentration measured by the HemoCue device; SpHb, Hemoglobin concentration measured by the Rad 67; True normal, test detected patients without anemia; True anemia, test detected patients with anemia; False normal; Test did not detect anemia; False anemia, not anemic patients were detected as anemic patients by the test; PPV, positive predictive value; NPV, negative predictive value.

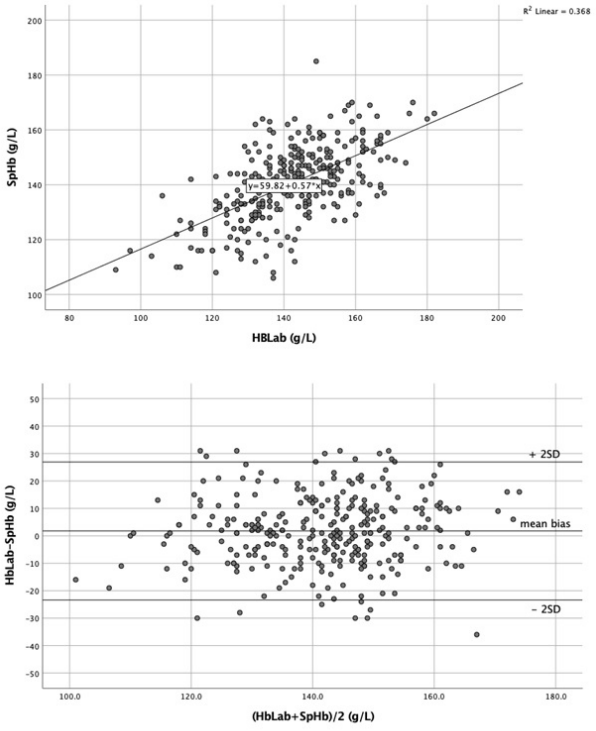

Fig. 2. — A, correlation of the Masimo-RAD67 hemoglobin measurements versus hemoglobin values measured in the laboratory. B, Bland-Altmann plot for the hemoglobin determination with the Masimo-RAD67 and the determination in the laboratory.

in non-anemic males and females was + 5.32 g/L and -0.40g/L, respectively. Additionally, in anemic males and females, a mean bias of Hb_{Lab} and SpHb of – 8.83g/L and – 8.56g/L was found. This finding suggests detection of falsely low hemoglobin values in non-anemic males and falsely high values in anemic patients by the SpHb. Detection of falsely low values in the high range and falsely high values in the low range Hb concentration by SpHb has also been reported during investigation of other Pulse CO-Oximeters (14-16). These findings could be explained by the site of venous blood sampling. Morris et al have shown in one individual a 6.3% difference between capillary blood samples drawn from the left and right hand (17). In our study, whole blood was drawn from the cephalic vein of the opposite arm, where the difference to the other side could possibly be considered much lower. Another reason might be the used rainbow® DCI®-mini Sensor of the Rad 67™ itself, in which the effect of ambient light cannot be completely ruled out. A black protective cover pulled over the sensor could prevent the effects of ambient light. However, this is not provided by the manufacturer for the rainbow® DCI®-mini sensor. Since the patients investigated in this study had all taken place on a deckchair, unforeseen patient movements as a further possible confounder could be most likely ruled out. Nail polish was removed before the sensor was attached. However, the event of an irregular heart rhythm would have had significant impact on the SpHb measurement, but was not explored in this investigation. Additionally, all measurement methodologies including so-called laboratory standard procedures have inherent variations and hemoglobin values will consistently differ within and between various invasive laboratory analyzers. In the same patient, Gehring et al reported a bias of

3g/L and SD of ± 2g/L between the hemoglobin-cyanide (HiCN) and a hematology analyzer (18). Additionally, a comparison between the HiCN method and a blood gas analyzer showed a bias of -2g/L an SD of ±3g/L. The impact of methemoglobin > 1% is questionable, as MetHb concentration was only determined with the Rad-67 and not in the laboratory. According to the recommendations of the manufacturer, SpHb values are considered to be no longer reliably measured if the detected MetHb content is > 2%.

With a cut off value of 130g/L for males and 120g/L for females, sensitivity/specificity of $Hb_{Hemocue}$ and SpHb to detect anemia were moderate with 75.0/100% and 75.0/95.2% for males and 88.9/98.9% and 66.7/91.1% for females, respectively. However, in males the PPV for anemia of the $Hb_{Hemocue}$ was excellent with 100% compared to 56.3% of the SpHb. In females, the PPV for anemia was only moderate with 80.0% for the $Hb_{Hemocue}$, but poor for the SpHb with 33.3.%. The finding of the less accurate identification of low hemoglobin levels by the SpHb especially in females confirms the results of investigations with other Pulse CO-oximeter devices. In 256 patients of a pre-anesthetic assessment clinic, Khalafallah et al. compared SpHb of the Masimo Pronto-7 device with Hb concentrations measured in the laboratory and reported a sensitivity to detect anemia of 57.1% for SpHb in females compared to 91.8% in males (19). Similar to our results they found significantly higher PI values in males compared to females, which might hint to a possible impact of the PI on the less precise anemia detection of the SpHb in females. The high rate of false positive anemia detection with the SpHb compared to the $Hb_{Hemocue}$ is remarkable. In total, false positive anemia detection was found with the $Hb_{Hemocue}$ in only two female patients compared to 19 patients (7 males and 12 females) using SpHb. While the false positive anemia detection of the $Hb_{Hemocue}$ was caused by a deviation of only 1g/L in each of the three patients, deviations of > 10g/L were found with the SpHb. Indeed, false positive anemia detection by SpHb was found in 4.5% of males and 8.9% of females, which is significantly lower than the results reported by Khalafallah et al, who found false positive anemia detection of SpHb using the Masimo Pronto-7 device in 19.1% of males and 15.6% of females (19).

However, both the $Hb_{Hemocue}$ and SpHb were useful for identification of preoperative non-anemic patients. Specificity and NPV were high in both devices.

Limitations of the study

The hemoglobin measurement of the HemoCue® using the modified Vanzetti's azide technique is from the methodological point of view largely similar to the cyanide-free Sodium Lauryl Sulphate (SLS) method of the laboratory analyzer XN 9000. For both, the HemoCue® and the XN 9000, the reliability against the HiCN-Method has been demonstrated (5-8). Methemoglobin concentration was not determined in the laboratory. Feiner et al. demonstrated an accuracy and precision of MetHb measured with the Radical 7 device of 1.9% ± 2.5% only in the 95-100% SaO_2 range (20). However, the Radical-7 readings become progressively more inaccurate as SaO_2 decreases < 95%, at times overestimating true values by 10 to 40%. In 22 patients (7.2%) in this study, SaO_2-values < 95% were measured. However, the impact of this proportion of patients is negligible. Irregular heart rhythm was not recorded in this investigation. Especially, in the elderly patients, atrial fibrillation is common and irregular heart rate causes a considerable variation of the pulse wave. In this study, 20.4% of the patients were older than 70 years and the prevalence of atrial fibrillation in this age group is nearly 11% for males and 5% for females. The exclusion for analysis of this population might have influenced the results for the SpHb measurement. The Rad-67 is not approved for patients with pre-existing renal failure. This population was not evaluated and therefore not excluded. Finally, all laboratory measurement methodologies have inherent variations and hemoglobin values will consistently differ within and between various invasive laboratory analyzers.

In conclusion, both devices reliably detected non-anemic patients. Linear correlation and agreement of Hb_{Lab} with $Hb_{Hemocue}$ were better than for SpHb. For both devices, anemia detection was moderate, but the positive prediction value for anemia was much better with the $Hb_{Hemocue}$. The current version of the Spot Check Rad-67™ Pulse CO-Oximeter® needs additional refinements to further improve its performance and reliability, before it can used as the sole basis for preoperative anemia screening.

References

1. Kehlet H. and Wilmore D.W. 2002. Multimodal strategies to improve surgical outcome. Am J Surg. 183(6):630-641.
2. Goodnough L.T., Maniatis A., Enshaw P., Benoni G., Beris P. and Bisbe E., et al. 2011. Detection, evaluation,

and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines. Br J Anaesth.106(1):13-22.
3. Gruson K.I., Aharonoff G.B., Egol K.A., Zuckerman J.D. and Koval K.J. 2020. The relationship between admission hemoglobin level and outcome after hip fracture. J Orthop Trauma. 16(1):39-44.
4. Froessler B., Rueger A.M. and Connolly M.P. 2018. Assessing the costs and benefits of perioperative iron deficiency anemia management with ferric carboxymaltose in Germany. Risk Manag Healthc Policy. 11:77-82.
5. Lewis S.M., Garvey B., Manning R., Sharp S.A. and Wardle J. 1991. Lauryl sulphate haemoglobin: a non-hazardous substitute for HiCN in haemoglobinometry. Clin Lab Haematol. 13(3):279-290.
6. Karsan A., Maclaren I., Conn D. and Wadsworth L. 1993. An evaluation of hemoglobin determination using sodium lauryl sulfate. Am J Clin Pathol. 100(2):123-126.
7. Harris N., Jou J.M., Devoto G., Lotz J., Pappas J. and Wranovics D., et al. 2005. Performance evaluation of the ADVIA 2120 hematology analyzer: an international multicenter clinical trial. Lab Hematol. 11(1):62-70.
8. Kalyan Chakravarthy V., Naveen Chandra D., Santhoshi Prasanna B., Jaya Mastan Rao T. and Ranga Rao D. 2012. Haemoglobin Estimation by Non-cyanide Methods. Journal of Clinical and Diagnostic Research. 6:6. 955-958.
9. Organization WH. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. 2011; https://www.who.int/vmnis/indicators/haemoglobin/en/. Accessed 15.05.2020.
10. Bland J.M. and Altman D.G. 1986. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1(8476):307-310.
11. Munoz M., Gomez-Ramirez S., Campos A., Ruiz J. and Liumbruno G.M. 2015. Pre-operative anaemia: prevalence, consequences and approaches to management. Blood Transfus. 13(3):370-379.
12. Knutson T., Della-Giustina D., Tomich E., Wills B., Luerssen E. and Reynolds P. 2013. Evaluation of a new nonnvasive device in determining hemoglobin levels in emergency department patients. West J Emerg Med. 14(3):283-286.
13. Gayat E., Aulagnier J., Matthieu E., Boisson M. and Fischler M. 2012. Non-invasive measurement of hemoglobin: assessment of two different point-of-care technologies. PLoS One. 7(1):e30065.
14. Baulig W., Seifert B., Spahn D.R. and Theusinger O.M. 2017. Accuracy of non-invasive continuous total hemoglobin measurement by Pulse CO-Oximetry in severe traumatized and surgical bleeding patients. J Clin Monit Comput. 31(1):177-185.
15. Tsuei B.J., Hanseman D.J., Blakeman M.J., Blakeman T.C., Yang S.H. and Branson R.D., et al. 2014. Accuracy of noninvasive hemoglobin monitoring in patients at risk for hemorrhage. *J* Trauma Acute Care Surg. 77(3 Suppl 2):134-139.
16. Vos J.J., Kalmar A.F., Struys M.M., Porte R.J., Wietasch J.K. and Scheeren T.W. 2012. Accuracy of non-invasive measurement of haemoglobin concentration by pulse co-oximetry during steady-state and dynamic conditions in liver surgery. Br J Anaesth. 109(4):522-528.
17. Morris S.S., Ruel M.T., Cohen R.J., Dewey K.G., de la Briere B. and Hassan M.N. 1996. Precision, accuracy, and reliability of hemoglobin assessment with use of capillary blood. Am J Clin Nutr. 69(6):1243-1248.
18. Gehring H., Hornberger C., Dibbelt L., Rothsigkeit A., Gerlach K., Schumacher J. and Schmucker P. 2002. Accuracy of point-of-care-testing (POCT) for determining hemoglobin concentrations. Acta Anaesthesiol Scand. 46(8):980-986.
19. Khalafallah A.A., Chilvers C.R., Thomas M., Chilvers C.M., Sexton M., Vialle M. and Robertson I.K. 2015. Usefulness of non-invasive spectrophotometric haemoglobin estimation for detecting low haemoglobin levels when compared with a standard laboratory assay for preoperative assessment. Br J Anaesth. 114(4):669-676.
20. Feiner J.R., Bickler P.E. and Mannheimer P.D. 2010. Accuracy of methemoglobin detection by pulse CO-oximetry during hypoxia. Anesth Analg.111(1):143-148.

(Acta Anaesth. Belg., 2020, 71, 131-136)

A survey of anesthetists' experience and perspectives of perioperative anaphylaxis at an Australian tertiary hospital

G. Chawla (*), A. Harrocks (**), P. Casey (**), E. McLellan (**), V. Eley (***)

Abstract : *Background :* Anaphylaxis is a life-threatening emergency that requires prompt recognition and institution of life-saving therapy. Perioperative Anaphylaxis Management Guidelines have been developed by the Australian and New Zealand College of Anaesthetists and Australian and New Zealand Anaesthetic Allergy Group and anesthetic societies worldwide to facilitate diagnosis and management of this rare, but severe complication.
Objectives : To perform a cross-sectional survey of the anesthetists' experience of perioperative anaphylaxis at a single centre and its effect on their practice.
Design : Survey questionnaire constructed in Survey Monkey® and sent via e-mail link to all anesthetists. This questionnaire included qualitative and quantitative questions.
Setting : Royal Brisbane and Women's Hospital, a tertiary referral hospital in Queensland.
Methods : Anesthetic specialists and provisional fellows at The Royal Brisbane and Women's Hospital were surveyed using an online platform regarding their experiences of managing anaphylaxis, referral for testing, formal incident reporting and knowledge of existing departmental protocol. We also asked if their experience of anaphylaxis modified their clinical practice.
Results : Forty-five out of 102 *(*44%) of the specialists and provisional fellows surveyed responded. Of these, 17 (38%) had been involved as primary anesthetist and 20 (44.5%) indirectly in at least one suspected case of perioperative anaphylaxis in the past 12-months. Most anesthetists were aware of the resources available in this crisis and appropriate referral for testing had occurred. There was poor local and national reporting of anaphylaxis as a critical incident.
Conclusion : A large percentage of the anesthetists surveyed had seen a case of perioperative anaphylaxis in the past year. Managing this life-threatening event has led to practice change for many anesthetists. There is a requirement for further education around incident reporting.

Key words : Anaphylaxis ; perioperative ; allergy ; adverse reaction ; anesthetic.

Introduction

Anaphylaxis is a potentially life threatening, severe allergic reaction as defined by the Australasian Society for Clinical Immunology and Allergy. Definitions vary in their wording, but worldwide, authorities agree that anaphylactic reactions represent severe and unexpected allergic reactions. Allergies are the fastest growing chronic disease in Australia and perhaps many other areas of the world. These include food, insect and drug allergies (including life threatening anaphylactic reactions) as well as atopic conditions such as asthma, eczema and allergic rhinitis. Within Australia alone, approximately 4 million people (20% of the population) have at least one allergic disease (1). It is predicted that by 2050 the number of patients affected by allergic diseases in Australia will increase by 70% to 7.7 million (1).

The incidence of allergic reactions during anesthesia varies by country, representing between 9 to 19% of reported anesthesia complications. In Australia these occur between 1 in 10,000 to 1 in 20,000 (2) anesthetics. In the 10th triennial anesthesia mortality report for Australia and New Zealand for the period of 2012-14, 7 of the 23 direct

Gunjan Chawla, MBBS, DA, FRCA, FANZCA ; Annabelle Harrocks, BSc, MBBCh, FANZCA ; Peter Casey, BPharm, MBBS, FANZCA ; Elizabeth McLellan, BSc, MBBS, FANZCA, Victoria Eley, BMed Sci, MBBS(Hons), FANZCA, PhD
(*) Caboolture Hospital (formerly at The Royal Brisbane and Women's Hospital) and, Faculty of Medicine, The University of Queensland, Australia
(**) Royal Brisbane & Women's Hospital, Australia
(***) Royal Brisbane & Women's Hospital and Faculty of Medicine, The University of Queensland, Australia
Corresponding author : G. Chawla, Department of Anaesthesia, Caboolture Hospital, McKean Street, Caboolture, QLD, Australia.
Email : doc_gunjan@yahoo.com

Paper submitted on April 15, 2020 and accepted on September 3, 2020
Conflict of interest : None

anesthesia related deaths were due to anaphylaxis (3). The mortality rate related to anaphylaxis under anesthesia is believed to be up to 9% (4-8). However, data from Western Australia show a much lower perioperative anaphylaxis mortality (0-1.4%) than quoted elsewhere (9). In 2016, Perioperative Anaphylaxis Management Guidelines were published by the Australian and New Zealand College of Anaesthetists (ANZCA) and Australian and New Zealand Anaesthetic Allergy Group (ANZAAG) to facilitate diagnosis and recommend strategies for anaphylaxis management (10). Gibbs et al. state that the lower mortality, though similar perioperative anaphylaxis rate reported by Western Australia maybe present in other developed countries, reflecting newer data with the overall decrease in perioperative mortality. Improved education, guidelines, anaphylaxis management being a professional development education activity compulsory for anesthetists in Australia and use of simulation for training in management of anesthetic crises could also contribute to improved outcomes.

Agents most likely to cause anaphylaxis vary between countries, according to variation in drug usage (8, 11, 12). For instance there is a higher proportion of anaphylactic reactions attributed to neuromuscular blocking agents (NMBAs) in France, Australia and New Zealand (6, 13-15) compared with Sweden, Denmark, and USA (16-18). Different patterns of antibiotic use influenced by institutional or national surgical prophylaxis guidelines also influence intraoperative anaphylaxis rates. Teicoplanin is recommended in surgical antibiotic prophylaxis guidelines in the United Kingdom and is the most common antibiotic cause of anaphylaxis in that region. Conversely, cephalosporins are widely used in France and are the most common antibiotic culprit in that country (13). Regional differences in experience of anaphylaxis and the culprit agents point to the benefit of epidemiological surveys (8). Worldwide collaboration would facilitate education and improve patient care both via preventive and treatment strategies.

Knowledge of anaphylaxis, experiences and practice preferences have been studied in several physician groups including allergy and immunology specialists, emergency physicians, family practitioners and pediatricians. Recently, the Royal College of Anaesthetists, UK published the 6th National Audit Project on Perioperative Anaphylaxis (NAP6) (19). This included a baseline survey of over 11,000 anesthetists from 341 hospitals in the UK exploring their experience, perspectives and knowledge regarding the management of perioperative anaphylaxis (20). No similar survey has been undertaken in Australia.

Our survey of anesthetists from a single tertiary institution in Australia, aimed to assess their experiences of managing anaphylaxis, referral for testing, formal incident reporting and knowledge of existing departmental protocol. We also asked if their experience of anaphylaxis modified their clinical practice.

Materials and Methods

This survey was undertaken at the Royal Brisbane and Women's Hospital (RBWH), a tertiary referral hospital in Queensland with close to 1000 beds. Ethics approval was obtained from the Royal Brisbane and Women's Hospital Ethics Committee (chaired by Dr G McGurk) on 7th November 2018 (LNR/2018/QRBW/47057). The survey was carried out over the period of December 2018 to January 2019. The survey questionnaire was constructed in Survey Monkey® and then sent via e-mail to all the anesthetists including anesthesia specialists and provisional fellows (fifth year of the five-year anesthetic training program) in the Department of Anesthesia and Perioperative Medicine at the RBWH. The department provides perioperative allergy testing and receives referrals from the hospitals in the Metro North Health Service, Queensland. There is a designated lead anesthetist for anaphylaxis and "Anaphylaxis Boxes" are provided in the operating theatre complex, consistent with ANZAAG Guidelines (10). The department runs educational activities and training sessions in the management of anaphylaxis.

Consent was implied by completion of the survey. The questionnaire was based on the NAP 6 baseline survey (Appendix 1) and consisted of three sections. The first section related to personal experience of anaphylaxis. This included the number of cases seen by the anesthetist over the last 12 months as the primary or principal anesthetist and cases which they assisted in the care of. This number was not used to infer the total number of cases seen, in case of duplication, but used to gather information about the experience alone. Participants were asked about referral for investigation and reporting of the event at the local level (RiskMan and PRIME hospital incident reporting) as well as in the Australian and New Zealand Tripartite Anaesthetic Data Committee web-based anesthetic incident recording system (WebAIRS). They were also asked about the probable and confirmed (if any) cause of anaphylactic reaction. The data for referral

and reporting were interpreted using the numbers for primary anesthetists' alone. The second section of the questionnaire related to participants' knowledge of local resources for the management and follow-up of patients with suspected anaphylaxis. This included the presence of anaphylaxis boxes in the operating theatre and awareness of the departmental lead anesthetist for anaphylaxis. The last section of the questionnaire included questions to determine whether the participants' experience of anaphylaxis had influenced their clinical practice. Participants were asked to answer by free-text response if they avoided any particular drug(s) in their clinical practice and to give reasons for avoidance. Responses were transcribed verbatim. Unanswered questions were not included in the calculations for the responses i.e. data were interpreted with the appropriate number of responses as baseline rather than discarding the entire response or using imputation.

Statistical analysis

This was a sample of convenience, with the population consisting of all anesthesia specialists and provisional fellows within the Department of Anesthesia and Perioperative Medicine. Data were analyzed using descriptive statistics. Survey responses were presented using number (percent). Free text responses were presented unedited.

Results

The survey was sent to 102 anesthetists and 45 (44%) responded. The population sampled included 92 (90%) anesthesia specialists and 10 (10%) provisional fellows. The duration of experience ranged from less than 6 months to more than 30 years.

Twenty-five (56%) respondents had been present during an episode of perioperative anaphylaxis in the past 12 months. Table I shows the involvement of the anesthetist as the primary (20 episodes, 17 anesthetists) or assisting anesthetist in cases of anaphylaxis.

The agents suspected at the time of the reaction included antibiotics, muscle relaxants, patent blue dye, ranitidine and blood products. A total of 20 incidents of suspected perioperative anaphylaxis were identified. Patients from 19 (95%) out of 20 episodes (as reported by primary anesthetist) had been referred for allergy testing. The primary anesthetist was aware of the confirmed agent in 14 (74%) of the 19 cases referred for allergy testing.

Table 1

Personal experience of case(s) of perioperative anaphylaxis in past 12-month period

As primary anesthetist:		As supporting anesthetist:	
1 case	14	1 case	11
2 cases	3	2 cases	7
>2 cases	0	>2 cases	2

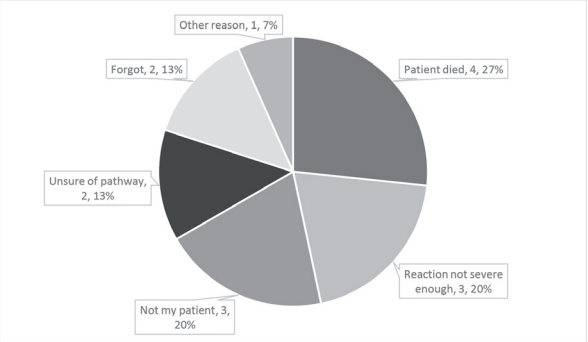

Fig. 1. – Reasons for lack of referring (15 responses)-possible barriers to referring and reporting.

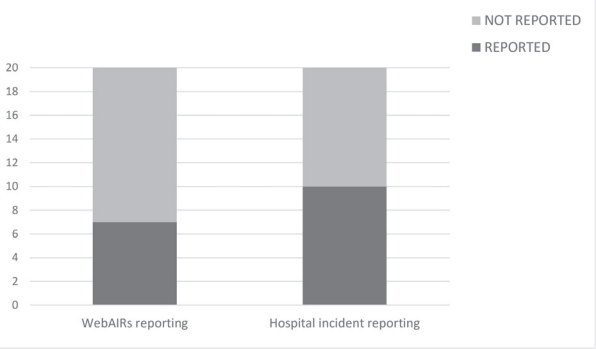

Fig. 2. – Reporting of cases of anaphylaxis (20 cases in total) at hospital level and via web-based anesthetic incident recording system (WebAIRS).

Figure 1 shows the reasons given (if any) for lack of reporting of the incident.

Figure 2 shows the numbers of cases reported on webAIRs and the hospital incident reporting system.

Forty-four (97%) out of 45 anesthetists were aware of anaphylaxis management guidelines and 43 (95%) of the labelled anaphylaxis boxes available in the theatre complex. Thirty-five anesthetists (78%) were aware of the departmental lead for perioperative anaphylaxis.

Fourteen (31%) anesthetists reported avoiding certain drugs or substances in their clinical practice due to the perceived high risk of anaphylaxis. These include neuromuscular blockers and teicoplanin.

The reasons given by anesthetists for avoiding certain drugs are shown in Table II as free text comments. Twenty-seven (60%) anesthetists perceived neuromuscular blockers to have the highest rate of perioperative anaphylaxis, while 17 (38%) believed this to be antibiotics and 1 (2%) patent blue dye. Five (11%) routinely administered a test dose of antibiotics and 1 (2%) used a test dose based on patient history.

Discussion

Despite intraoperative anaphylaxis being considered a rare event, over one half of the respondents to our survey had witnessed a case of perioperative anaphylaxis in the preceding 12 months. Suspected cases were appropriately referred for investigation i.e. allergy testing and follow up. There was inconsistent formal incident reporting to webAIRs and the hospital incident reporting system. The reasons for failing to report were consistent with reported institutional and process barriers (21-24). The awareness of the guidelines and local arrangements among our survey population were excellent. Witnessing an episode of anaphylaxis, case reports in journals or presentations at morbidity and mortality meetings were among the factors that have modified the practice of anesthetists. These are listed in table II. Few anesthetists reported using a test dose prior to administration of antibiotics.

When compared with the results of NAP6 (19), our population demonstrated higher awareness of and access to management guidelines and anaphylaxis packs. The percentage of patients referred for investigation were higher at our hospital, which may reflect the availability of on-site expertise and allergy testing. As clinicians we shape our actions based on our own and others' experiences, evidence in peer-reviewed journals and guidelines from national and international specialty associations. Among anesthetists from both countries, neuromuscular blockers and antibiotics were the most common drugs avoided by clinicians who had experienced perioperative anaphylaxis. Similar beliefs existed among both populations, regarding the most common causes of anaphylaxis.

Nearly one-third of UK anesthetists (32%) reported routinely using a test dose when administering intravenous antibiotics which is much higher than in our population. There is little scientific evidence to support the administration of a test dose and it would seem that the routine use of a test dose is likely to be influenced by institutional or national practices though a lot of individual variation exists. In practice, a typical 'test dose' given in the context of perioperative prophylaxis would be 1-2mls of the antibiotic preparation which is far in excess of doses used in the setting of allergy testing or desensitization. In fact NAP6 (6) reported that test doses were responsible for anaphylactic reactions as well and there was no reduction in severity noted with lower doses. One of the recommendations from Harper et al was the administration of antibiotics several minutes prior to induction of anesthesia to increase safety by confirmation of allergy status, decreased physiological derangement and clear indication of the causative agent (6).

Table II

Reasons for avoiding certain drugs: Comments from 13 anesthetists who responded "Yes" to the question: "Do you generally try to avoid any particular drug/substance as a result of perceived high risk of anaphylaxis?" (1 missing)

Heard of several cases (2 respondents)
Death, severe anaphylaxis associated
To reduce risk (of anaphylaxis)
High incidence based on journal articles
Published anaphylaxis rates compared to other effective agents
High institutional rate
Personal experience
Morbidity and mortality meetings
I try to limit use of suxamethonium to genuine needs-based use due to a higher rate of anaphylaxis
The less we do, the less potential problems we cause. I only paralyse when there is a surgical indication or for example the patient had rocuronium before. I perceive that as a good strategy to reduce the risk of anaphylaxis and traumatic recall. Intubation does not require paralysis
Suxamethonium / Rocuronium- higher risk. Avoid muscle relaxants if possible.

Limitations

This survey was limited by the fact that it was conducted at a single centre, the population surveyed was small and the response rate less than 50%. The RBWH is a tertiary institution and the resources and services may vary from those in regional hospitals within Queensland and those in other states in Australia. Selection bias may have occurred, with participating anesthetists interested in sharing their experience following a case of anaphylaxis. This may account for the high proportion of anesthetists who had witnessed a case in the previous 12-month period.

Conclusion

Our survey identified appropriate knowledge among anesthetists and consistent referral of patients

for skin testing. However, there was poor local and national reporting of anaphylaxis as a critical incident, an area which can be improved. This survey does not reflect the practice of anesthetists Australia-wide and a national survey could guide dissemination of knowledge and resources. A larger survey would take into account regional and institutional differences including resources and facilities for training of anesthetists and the availability of allergy testing. Likewise, surveys done in institutions worldwide could guide the training of anesthetists to deal with perioperative anaphylaxis and help standardize resources and protocols to improve patient care.

References

1. Mullins R.J., Cook M., Douglass J., Mallon D., Smith J.and Wong M. 2007.The economic impact of allergic disease in Australia : not to be sneezed at. ASCIA/Access Economics Report,. Report. Australia : Australasian Society of Clinical Immunology and Allergy.
2. Fisher M.M.and Baldo B.A. 1993. The incidence and clinical features of anaphylactic reactions during anesthesia in Australia. Ann Fr Anesth Reanim. 12(2):97-104.
3. Safety of Anaesthesia: A review of anaesthesia-related mortality reporting in Australia and New Zealand 2012-2014. Australia: Australian and New Zealand College of Anaesthetists, Sub-Committee M; 2017.
4. Mertes P.M., Malinovsky J.M., Jouffroy L., Working Group of The S., Sfa, Aberer W. et al. 2011. Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. J Investig Allergol Clin Immunol. 21(6):442-53.
5. Mertes P.M., Laxenaire M.C., Lienhart A., Aberer W., Ring J. and Pichler W.J., et al. 2005. Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. J Investig Allergol Clin Immunol. 15(2):91-101.
6. Harper N.J.N., Cook T.M., Garcez T., Farmer L., Floss K. and Marinho S., et al. 2018. Anaesthesia, surgery, and life-threatening allergic reactions: epidemiology and clinical features of perioperative anaphylaxis in the 6th National Audit Project (NAP6). Br J Anaesth. 121(1):159-71.
7. Reitter M., Petitpain N., Latarche C., Cottin J., Massy N. and Demoly P., et al. 2014. Fatal anaphylaxis with neuromuscular blocking agents: a risk factor and management analysis. Allergy. 69(7):954-9.
8. Mertes P.M., Ebo D.G., Garcez T., Rose M., Sabato V. and Takazawa T., et al. 2019. Comparative epidemiology of suspected perioperative hypersensitivity reactions. Br J Anaesth. 123(1):e16-e28.
9. Gibbs N.M., Sadleir P.H., Clarke R.C. and Platt P.R. 2013. Survival from perioperative anaphylaxis in Western Australia 2000-2009. Br J Anaesth. 111(4):589-93.
10. Kolawole H., Marshall S.D., Crilly H., Kerridge R. and Roessler P. 2017. Australian and New Zealand Anaesthetic Allergy Group/Australian and New Zealand College of Anaesthetists Perioperative Anaphylaxis Management Guidelines. Anaesth Intensive Care. 45(2):151-8.
11. Florvaag E. and Johansson S.G. 2009. The pholcodine story. Immunol Allergy Clin North Am. 29(3):419-27.
12. Florvaag E., Johansson S.G., Irgens A. and De Pater G.H. 2011. IgE-sensitization to the cough suppressant pholcodine and the effects of its withdrawal from the Norwegian market. Allergy. 66(7):955-60.
13. Tacquard C., Collange O., Gomis P., Malinovsky J.M., Petitpain N. and Demoly P., et al. 2017. Anaesthetic hypersensitivity reactions in France between 2011 and 2012: the 10th GERAP epidemiologic survey. Acta Anaesthesiol Scand. 61(3):290-9.
14. Mertes P.M., Alla F., Trechot P., Auroy Y., Jougla E. and Groupe D'etudes Des Reactions Anaphylactoides P. Anaphylaxis during anesthesia in France: an 8-year national survey. J Allergy Clin Immunol. 2011;128(2):366-73.
15. Sadleir P.H., Clarke R.C., Bunning D.L. and Platt P.R. 2013. Anaphylaxis to neuromuscular blocking drugs: incidence and cross-reactivity in Western Australia from 2002 to 2011. Br J Anaesth. 110(6):981-7.
16. Florvaag E., Johansson S.G., Oman H., Venemalm L., Degerbeck F. and Dybendal T., et al. 2005. Prevalence of IgE antibodies to morphine. Relation to the high and low incidences of NMBA anaphylaxis in Norway and Sweden, respectively. Acta Anaesthesiol Scand. 49(4):437-44.
17. Gurrieri C., Weingarten T.N., Martin D.P., Babovic N., Narr B.J. and Sprung J. et al. 2011. Allergic reactions during anesthesia at a large United States referral center. Anesth Analg. 113(5):1202-12.
18. Gonzalez-Estrada A., Pien L.C., Zell K., Wang X.F. and Lang D.M. 2015. Antibiotics are an important identifiable cause of perioperative anaphylaxis in the United States. J Allergy Clin Immunol Pract. 3(1):101-5 e1.
19. T. M.C. and N. H. 2018. Anaesthesia, Surgery and Life-Threatening Allergic Reactions Report and findings of the Royal College of Anaesthetists' 6th National Audit Project: Perioperative Anaphylaxis London: Royal College of Anaesthetists; May 2018. Contract No.: ISBN: 978-1-900936-18-7
20. Kemp H.I., Cook T.M., Thomas M. and Harper N.J.N. 2017. UK anaesthetists' perspectives and experiences of severe perioperative anaphylaxis: NAP6 baseline survey. Br J Anaesth. 119(1):132-9.
21. Kingston M.J., Evans S.M., Smith B.J.and Berry J.G. 2004. Attitudes of doctors and nurses towards incident reporting: a qualitative analysis. Med J Aust. 181(1):36-9.
22. Evans S.M., Berry J.G., Smith B.J., Esterman A., Selim P. and O'shaughnessy J. et al. 2006. Attitudes and barriers to incident reporting: a collaborative hospital study. Qual Saf Health Care. 15(1):39-43.
23. Fukuda H., Imanaka Y., Hirose M. and Hayashida K. 2010. Impact of system-level activities and reporting design on the number of incident reports for patient safety. Qual Saf Health Care. 2010;19(2):122-7.
24. Mahajan R.P. 2010. Critical incident reporting and learning. Br J Anaesth. 105(1):69-75.

Appendix 1.

Questionnaire:

Personal experience of perioperative anaphylaxis

1. In the last 12 months, how many cases of suspected perioperative anaphylaxis have you:
a. seen in patients directly under your care, i.e., where you anesthetized or sedated the patient?
b. assisted in the management of?

2. Of these cases (those you saw directly PLUS those you assisted with, i.e., combining answers to Q1 and Q2): what were the causes of each anaphylactic reaction? (Write "Don't know" if unknown)

3. How many cases did you (or someone from the primary anesthetic team):
a) Refer for investigation
b) Report via webAIRS?
c) Report via your hospital incident-reporting system?

4. If patients were not referred, it was because:
a) Patient died
b) Reaction not severe enough
c) Unsure about pathway
d) Forgot
e) Not my patient
f) Other

5. In how many cases was the diagnosis of anaphylaxis confirmed by subsequent investigation?

Local arrangements - if your next patient has a suspected anaphylactic reaction:

6. Please reply with "Yes/ No". Do you have:
a) immediate access to anaphylaxis guidelines in your theatre/ theatre complex?
b) a specific, labelled anaphylaxis pack (distinct from the usual emergency drug box) in your theatre or nearby?

7. Do you know the departmental lead anesthetist for perioperative anaphylaxis?

Personal attitudes to the risk of perioperative anaphylaxis

8. Personal practice:
a) Do you generally try to avoid any particular drug/substance as a result of perceived high risk of anaphylaxis?
b) If you answered yes to the question above, please explain the reasons why? (For example, personal experience, heard of several cases, information published in journals, etc.)

9. In your perception, which current perioperative drug (or other substance) has the highest rate of anaphylaxis associated with it? i.e., reactions per 1,000 doses.

10. Do you routinely administer a test dose of antibiotics?

10 vials 2 ml	864,43 €** 780,00 €*
10 vials 5 ml	2.146,55 €** 1.950,00 €*

THE BRIDION EFFECT:

RECOVERY FROM ANY DEPTH OF NMB

IN THE OR

IN THE PACU

IN PATIENTS AND PROCEDURES

THROUGHOUT THE HOSPITAL

Please read the full prescription leaflet, before prescribing.

* Ex-factory price without VAT ** Theoric Public Price

MSD Belgium BV/SRL
Lynx Binnenhof 5 Clos du Lynx
Brussel 1200 Bruxelles

bridion® sugammadex

PREDICTABLE. COMPLETE. RAPID.

BE-XBR-00109
Date of last revision 09/2020

1. NAAM VAN HET GENEESMIDDEL Bridion® 100 mg/ml oplossing voor injectie **2. KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING** 1 ml bevat sugammadex als natriumzout equivalent aan 100 mg sugammadex. Elke injectieflacon van 2 ml bevat natriumsugammadex equivalent aan 200 mg sugammadex. Elke injectieflacon van 5 ml bevat natriumsugammadex equivalent aan 500 mg sugammadex. Hulpstof(fen) met bekend effect: Bevat tot 9,7 mg/ml natrium (zie rubriek 4.4). Voor de volledige lijst van hulpstoffen, zie rubriek 6.1. **3. FARMACEUTISCHE VORM** Oplossing voor injectie (injectievloeistof). Een heldere en kleurloze tot lichtgele oplossing. De pH ligt tussen 7 en 8 en de osmolaliteit tussen 300 en 500 mOsm/kg. **4. KLINISCHE GEGEVENS 4.1 Therapeutische indicaties** Opheffing van de door rocuronium of vecuronium geïnduceerde neuromusculaire blokkade bij volwassenen. *Voor pediatrische patiënten:* bij kinderen en adolescenten van 2 t/m 17 jaar wordt het gebruik van sugammadex alleen aanbevolen bij standaardopheffing van een door rocuronium geïnduceerde neuromusculaire blokkade. **4.2 Dosering en wijze van toediening** Dosering Sugammadex mag alleen worden toegediend door of onder supervisie van een anesthesist. Het gebruik van een geschikte neuromusculaire monitortechniek wordt aanbevolen om het herstel van de neuromusculaire blokkade te bewaken (zie rubriek 4.4). De aanbevolen dosis sugammadex is afhankelijk van het niveau van de op te heffen neuromusculaire blokkade. De aanbevolen dosis is niet afhankelijk van de toegediende anesthesie. Sugammadex kan worden gebruikt voor opheffing van verschillende niveaus van door rocuronium of vecuronium geïnduceerde neuromusculaire blokkade: ***Volwassenen*** *Standaardopheffing:* Er wordt een dosis van 4 mg/kg sugammadex aanbevolen indien het herstel ten minste 1-2 posttetanische tellingen (PTC) heeft bereikt na een door rocuronium of vecuronium geïnduceerde blokkade. De mediane hersteltijd van de T4/T1-ratio tot 0,9 is ongeveer 3 minuten (zie rubriek 5.1). Een dosis van 2 mg/kg sugammadex wordt aanbevolen als spontaan herstel is opgetreden tot minimaal het terugkeren van T2 na een door rocuronium of vecuronium geïnduceerde blokkade. De mediane hersteltijd van de T4/T1-ratio tot 0,9 is ongeveer 2 minuten (zie rubriek 5.1). Het gebruik van de aanbevolen doses voor standaardopheffing na rocuronium zal ten opzichte van een door vecuronium geïnduceerde neuromusculaire blokkade leiden tot een iets snellere mediane hersteltijd van de T4/T1-ratio tot 0,9 (zie rubriek 5.1). *Onmiddellijke opheffing van een door rocuronium geïnduceerde blokkade:* Als er een klinische noodzaak bestaat voor onmiddellijke opheffing na toediening van rocuronium, wordt een dosis van 16 mg/kg sugammadex aanbevolen. Als 16 mg/kg sugammadex 3 minuten na een bolusdosis van 1,2 mg/kg rocuroniumbromide wordt toegediend, kan een mediane hersteltijd van de T4/T1-ratio tot 0,9 van ongeveer 1,5 minuten worden verwacht (zie rubriek 5.1). Er zijn geen gegevens beschikbaar die het gebruik van sugammadex aanbevelen voor onmiddellijke opheffing na een door vecuronium geïnduceerde blokkade. *Hernieuwde toediening van sugammadex*: In de uitzonderlijke situatie dat zich postoperatief, na een initiële dosis van 2 mg/kg of 4 mg/kg sugammadex, opnieuw een neuromusculaire blokkade voordoet (zie rubriek 4.4), wordt een herhalingsdosis van 4 mg/kg sugammadex aanbevolen. Na een tweede dosis sugammadex moet de patiënt zorgvuldig gecontroleerd worden om er zeker van te zijn dat de neuromusculaire functie terugkeert. *Hernieuwde toediening van rocuronium of vecuronium na sugammadex:* Voor wachttijden voor hernieuwde toediening van rocuronium of vecuronium na opheffing met sugammadex, zie rubriek 4.4. **Aanvullende informatie met betrekking tot speciale patiëntengroepen** ***Nierfunctiestoornis:*** Het gebruik van sugammadex bij patiënten met een ernstige nierfunctiestoornis (waaronder dialysepatiënten (creatinineklaring < 30 ml/min)) wordt niet aanbevolen (zie rubriek 4.4). Studies bij patiënten met een ernstige nierfunctiestoornis hebben onvoldoende veiligheidsgegevens gegenereerd om het gebruik van sugammadex bij deze patiënten te ondersteunen (zie ook rubriek 5.1). Bij lichte en matige nierfunctiestoornis (creatinineklaring ≥ 30 en < 80 ml/min): de dosisaanbevelingen zijn dezelfde als voor volwassenen zonder nierfunctiestoornis. ***Ouderen:*** Na toediening van sugammadex bij terugkeer van T2 na een door rocuronium geïnduceerde blokkade was de mediane hersteltijd van de T4/T1-ratio tot 0,9 bij volwassenen (18-64 jaar) 2,2 minuten, bij ouderen (65-74 jaar) 2,6 minuten en bij zeer oude patiënten (75 jaar of ouder) 3,6 minuten. Hoewel bij ouderen het herstel vaak trager optreedt, dient dezelfde dosisaanbeveling als voor volwassenen te worden aangehouden (zie rubriek 4.4). ***Patiënten met obesitas:*** Bij patiënten met obesitas, waaronder patiënten met morbide obesitas (body mass index ≥ 40 kg/m2), dient de dosering van sugammadex te worden gebaseerd op het feitelijke lichaamsgewicht. Dezelfde dosisaanbevelingen als voor volwassenen dienen te worden aangehouden. ***Leverfunctiestoornis:*** Er zijn geen studies gedaan bij patiënten met een leverfunctiestoornis. Voorzichtigheid moet worden betracht wanneer gebruik van sugammadex overwogen wordt bij patiënten met een ernstige leverfunctiestoornis of wanneer de patiënt naast de leverfunctiestoornis ook coagulopathie heeft (zie rubriek 4.4). Bij lichte tot matige leverfunctiestoornis: aangezien sugammadex voornamelijk renaal wordt uitgescheiden, zijn er geen dosisaanpassingen vereist. ***Pediatrische patiënten*** De gegevens betreffende pediatrische patiënten zijn beperkt (slechts één studie gericht op opheffing van een door rocuronium geïnduceerde neuromusculaire blokkade, bij terugkeer van T2). *Kinderen en adolescenten:* Bij kinderen en adolescenten (2 t/m 17 jaar) wordt voor standaardopheffing bij terugkeer van T2 na een door rocuronium geïnduceerde blokkade 2 mg/kg sugammadex aanbevolen. Bridion 100 mg/ml kan worden verdund tot 10 mg/ml ten behoeve van een betere nauwkeurigheid van de dosering bij pediatrische patiënten (zie rubriek 6.6). Andere situaties van standaardopheffing zijn niet onderzocht en worden daarom niet aanbevolen totdat nadere gegevens beschikbaar komen. Onmiddellijke opheffing is bij kinderen en adolescenten niet onderzocht en wordt daarom niet aanbevolen totdat nadere gegevens beschikbaar komen. *Voldragen pasgeborenen en zuigelingen:* De ervaring met het gebruik van sugammadex bij zuigelingen (30 dagen tot 2 jaar) is beperkt en voldragen pasgeborenen (jonger dan 30 dagen) zijn niet onderzocht. Het gebruik van sugammadex bij voldragen pasgeborenen en zuigelingen wordt daarom niet aanbevolen totdat nadere gegevens beschikbaar komen. **Wijze van toediening** Sugammadex dient intraveneus te worden toegediend als eenmalige bolusinjectie. De bolusinjectie moet snel worden gegeven, binnen 10 seconden, in een bestaande intraveneuze lijn (zie rubriek 6.6). Sugammadex is in klinische onderzoeken uitsluitend als eenmalige bolusinjectie toegediend. **4.3 Contra-indicaties** Overgevoeligheid voor de werkzame stof of voor een van de in rubriek 6.1 vermelde hulpstof(fen). **4.8 Bijwerkingen** ***Samenvatting van het veiligheidsprofiel*** Bridion wordt gelijktijdig toegediend met neuromusculair blokkerende stoffen en anesthetica bij operatiepatiënten. De causaliteit van bijwerkingen is daarom moeilijk te bepalen. De meest gerapporteerde bijwerkingen bij patiënten die een chirurgische ingreep ondergingen waren hoest, luchtwegcomplicatie van anesthesie, complicaties bij anesthesie, hypotensie ten gevolge van een verrichting en verrichtingscomplicatie (Vaak (≥ 1/100, < 1/10)). ***Tabel 2: Tabel met bijwerkingen*** De veiligheid van sugammadex is beoordeeld bij 3519 unieke patiënten in een gepoolde fase I-III veiligheidsdatabase. De volgende bijwerkingen zijn gemeld in placebogecontroleerde onderzoeken waarbij patiënten anesthesie en/of neuromusculair blokkerende stoffen kregen (1078 patiënten kregen sugammadex vs. 544 patiënten placebo): [Zeer vaak (≥ 1/10), vaak (≥ 1/100, < 1/10), soms (≥ 1/1000, < 1/100), zelden (≥ 1/10.000, < 1/1000), zeer zelden (< 1/10.000)]. Systeem/orgaanklasse/Frequenties/Bijwerkingen (voorkeursterm): Immuunsysteemaandoeningen Soms: Geneesmiddelenovergevoeligheidsreacties (zie rubriek 4.4). Ademhalingsstelsel-, borstkas- en mediastinumaandoeningen Vaak: Hoest. Letsels, intoxicaties en verrichtingscomplicaties Vaak: Luchtwegcomplicatie van anesthesie, Complicatie bij anesthesie (zie rubriek 4.4), Hypotensie ten gevolge van een verrichting, Verrichtingscomplicatie. ***Beschrijving van een aantal specifieke bijwerkingen*** Geneesmiddelenovergevoeligheid: Overgevoeligheidsreacties, waaronder anafylaxie, zijn waargenomen bij sommige patiënten en vrijwilligers (voor informatie over vrijwilligers, zie Informatie over gezonde vrijwilligers hieronder). In klinische onderzoeken bij patiënten die een chirurgische ingreep ondergingen zijn deze reacties soms gemeld; de postmarketingfrequentie waarin zij optreden is niet bekend. Deze reacties, die varieerden van geïsoleerde gevallen van huidreacties tot ernstige systemische reacties (d.w.z. anafylaxie, anafylactische shock), zijn ook voorgekomen bij patiënten die niet eerder blootgesteld waren aan sugammadex. Symptomen die geassocieerd kunnen zijn met deze reacties zijn: overmatig blozen, urticaria, erythemateuze huiduitslag, (ernstige) hypotensie, tachycardie, zwelling van de tong en keelholte, bronchospasme en obstructieve longaandoeningen. Ernstige overgevoeligheidsreacties kunnen fataal zijn. Luchtwegcomplicatie bij anesthesie: Luchtwegcomplicaties van anesthesie omvatten schokbewegingen tegen de beademingsbuis, hoest, lichte schokbeweging, arousal tijdens de operatie, hoesten tijdens de anesthesieprocedure of tijdens de operatie, of aan de anesthesieprocedure gerelateerde spontane ademhaling van de patiënt. Complicatie bij anesthesie: Complicaties bij anesthesie, indicatief voor herstel van de neuromusculaire functie, zijn beweging van een ledemaat of het lichaam of hoesten gedurende de anesthesieprocedure of gedurende de operatie, grimassen of zuigen op de beademingstube. Zie rubriek 4.4 lichte anesthesie. Verrichtingscomplicatie: Verrichtingscomplicaties omvatten hoest, tachycardie, bradycardie, bewegen, en versnelling van de hartslag. Ernstige bradycardie: Na het op de markt komen zijn binnen enkele minuten na toediening van sugammadex (zie rubriek 4.4) geïsoleerde gevallen van ernstige bradycardie en bradycardie met hartstilstand waargenomen. Hernieuwd optreden van een neuromusculaire blokkade: In klinische onderzoeken met patiënten die werden behandeld met rocuronium of vecuronium en bij wie een dosis sugammadex werd toegediend geschikt voor de diepte van de neuromusculaire blokkade (N=2022), werd een incidentie van 0,20 % waargenomen van hernieuwd optreden van de neuromusculaire blokkade gebaseerd op neuromusculaire monitoring of klinisch bewijs (zie rubriek 4.4). Informatie over gezonde vrijwilligers: Een gerandomiseerd, dubbelblind onderzoek heeft de incidentie van geneesmiddelgerelateerde overgevoeligheidsreacties onderzocht bij gezonde vrijwilligers die tot drie doses placebo (N=76), sugammadex 4 mg/kg (N=151) of sugammadex 16 mg/kg (N=148) kregen. Meldingen van vermoede overgevoeligheid werden beoordeeld door een geblindeerde (adjudicatie)commissie. De incidentie van beoordeelde overgevoeligheid was respectievelijk 1,3 %, 6,6 % en 9,5 % in de placebo-, de sugammadex 4 mg/kg- en de sugammadex 16 mg/kg-groep. Er waren geen meldingen van anafylaxie na placebo of sugammadex 4 mg/kg. Er was één enkel geval van beoordeelde anafylaxie na de eerste dosis sugammadex 16 mg/kg (incidentie 0,7 %). Er was geen bewijs van een verhoogde frequentie of ernst van overgevoeligheid met herhaalde doses sugammadex. In een eerder onderzoek met een zelfde opzet, waren er drie toegewezen gevallen van anafylaxie, alle na sugammadex 16 mg/kg (incidentie 2,0 %). In de gepoolde fase I-database zijn bijwerkingen die beschouwd worden als vaak (≥ 1/100, < 1/10) of zeer vaak (≥ 1/10) en frequenter bij proefpersonen behandeld met sugammadex dan in de placebogroep onder andere: dysgeusie (10,1 %), hoofdpijn (6,7 %), misselijkheid (5,6 %), urticaria (1,7 %), pruritus (1,7 %), duizeligheid (1,6 %), braken (1,2 %) en buikpijn (1,0 %). ***Aanvullende informatie met betrekking tot speciale patiëntengroepen*** **Longpatiënten:** In post-marketinggegevens en in één specifiek klinisch onderzoek bij patiënten met een voorgeschiedenis van longcomplicaties, werd bronchospasme gemeld als mogelijke bijwerking. Net als bij alle patiënten met een voorgeschiedenis van longcomplicaties, dient de arts zich bewust te zijn van het mogelijke optreden van bronchospasmen. **Pediatrische patiënten** Uit een beperkte database blijkt dat het veiligheidsprofiel van sugammadex (tot maximaal 4 mg/kg) bij pediatrische patiënten gelijk is aan dat bij volwassenen. **Patiënten met morbide obesitas** In één klinische studie gericht op patiënten met morbide obesitas was het bijwerkingenprofiel over het algemeen vergelijkbaar met het profiel bij volwassen patiënten in gepoolde fase 1 tot– 3-studies (zie tabel 2). ***Melding van vermoedelijke bijwerkingen*** Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem: **voor België**: Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten - Afdeling Vigilantie, Postbus 97, B-1000 Brussel Madou. Website: www.fagg.be, e-mail: adversedrugreactions@fagg-afmps.be. (Website: http://www.fagg-afmps.be, E-Mail: adversedrugreactions@fagg-afmps.be). **7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN** Merck Sharp & Dohme B.V., Waarderweg 39, 2031 BN Haarlem, Nederland. **8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN** EU/1/08/466/001, EU/1/08/466/002. **9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING** Datum van eerste verlening van de vergunning: 25 juli 2008, Datum van laatste verlenging: 21 juni 2013. **10. DATUM VAN HERZIENING VAN DE TEKST** 04/2020**. Legale status van aflevering:** ziekenhuisgebruik. Gedetailleerde informatie over dit geneesmiddel is beschikbaar op de website van het Europees Geneesmiddelenbureau (http://www.ema.europa.eu).

1. DENOMINATION DU MEDICAMENT Bridion® 100 mg/ml, solution injectable **2. COMPOSITION QUALITATIVE ET QUANTITATIVE** 1 ml contient l'équivalent de 100 mg de sugammadex sous forme de sugammadex sodique. Chaque flacon de 2 ml contient l'équivalent de 200 mg de sugammadex sous forme de sugammadex sodique. Chaque flacon de 5 ml contient l'équivalent de 500 mg de sugammadex sous forme de sugammadex sodique. Excipient(s) à effet notoire : Contient jusqu'à 9,7 mg/ml de sodium (voir rubrique 4.4). Pour la liste complète des excipients, voir rubrique 6.1. **3. FORME PHARMACEUTIQUE** Solution injectable (injection). Solution limpide, incolore à légèrement jaune. Le pH est compris entre 7 et 8 et l'osmolalité entre 300 et 500 mOsm/kg. **4. INFORMATIONS CLINIQUES 4.1 Indications thérapeutiques** Décurarisation chez l'adulte après bloc neuromusculaire induit par le rocuronium ou le vécuronium. *Population pédiatrique :* le sugammadex est recommandé uniquement pour la décurarisation en routine après un bloc neuromusculaire induit par le rocuronium chez l'enfant et l'adolescent âgés de 2 à 17 ans. **4.2 Posologie et mode d'administration** **Posologie** Le sugammadex ne doit être administré que par ou sous la surveillance d'un anesthésiste. L'utilisation d'une méthode appropriée de monitorage neuromusculaire est recommandée pour surveiller la récupération du bloc neuromusculaire (voir rubrique 4.4). La dose de sugammadex recommandée dépend du degré du bloc neuromusculaire à décurariser. La dose recommandée est indépendante du protocole anesthésique. Le sugammadex peut être utilisé pour décurariser différents degrés de bloc neuromusculaire induit par le rocuronium ou le vécuronium : ***Adultes*** *Décurarisation en routine :* Une dose de 4 mg/kg de sugammadex est recommandée après réapparition de 1 à 2 réponses minimum au Compte Post Tétanique (PTC) après un bloc neuromusculaire induit par le rocuronium ou le vécuronium. Le délai médian de récupération du rapport T_4/T_1 à 0,9 est alors d'environ 3 minutes (voir rubrique 5.1). Une dose de 2 mg/kg de sugammadex est recommandée après réapparition spontanée de la 2ème réponse au train-de-quatre (T2) après un bloc induit par le rocuronium ou le vécuronium. Le délai médian de récupération du rapport T_4/T_1 à 0,9 est alors d'environ 2 minutes (voir rubrique 5.1). L'utilisation des doses recommandées pour une décurarisation en routine conduit à un délai médian de récupération du rapport T_4/T_1 à 0,9 du bloc neuromusculaire induit par le rocuronium légèrement plus court comparativement au bloc neuromusculaire induit par le vécuronium (voir rubrique 5.1). *Décurarisation immédiate après un bloc induit par le rocuronium :* En cas de nécessité clinique d'une décurarisation immédiate après administration de rocuronium, une dose de 16 mg/kg de sugammadex est recommandée. L'administration de 16 mg/kg de sugammadex 3 minutes après une dose de 1,2 mg/kg de bromure de rocuronium permet une médiane de récupération attendue du rapport T_4/T_1 à 0,9 d'environ 1,5 minutes (voir rubrique 5.1). En l'absence de données, le sugammadex n'est pas recommandé pour une décurarisation immédiate après un bloc neuromusculaire induit par le vécuronium. *Nouvelle administration du sugammadex :* Dans le cas exceptionnel d'une récurrence du bloc neuromusculaire en post-opératoire (voir rubrique 4.4) après une dose initiale de 2 mg/kg ou de 4 mg/kg de sugammadex, il est recommandé d'administrer une dose supplémentaire de 4 mg/kg de sugammadex. Après l'administration de cette seconde dose de sugammadex, le patient devra être étroitement surveillé afin de s'assurer d'une récupération complète et stable de la fonction neuromusculaire. *Nouvelle administration de rocuronium ou de vécuronium après le sugammadex :* Pour les délais nécessaires avant une nouvelle administration de rocuronium ou de vécuronium après décurarisation par le sugammadex, voir rubrique 4.4. **Informations complémentaires concernant des populations particulières** ***Insuffisance rénale :*** L'utilisation du sugammadex chez les patients présentant une insuffisance rénale sévère (avec ou sans dialyse (CLCr < 30 ml/min)) n'est pas recommandée (voir rubrique 4.4). Les études réalisées chez les patients présentant une insuffisance rénale sévère n'ont pas fourni de données de sécurité suffisantes pour permettre l'utilisation du sugammadex chez ces patients (voir également la rubrique 5.1). Insuffisance rénale légère à modérée (clairance de la créatinine ≥ 30 et < 80 ml/min) : les doses recommandées sont les mêmes que celles recommandées chez les adultes sans insuffisance rénale. ***Sujets âgés :*** Après administration du sugammadex à la réapparition de la 2ème réponse au train-de-quatre (T_2) après un bloc neuromusculaire induit par le rocuronium, le délai médian de récupération du rapport T_4/T_1 à 0,9 a été alors de 2,2 minutes chez l'adulte (18-64 ans), 2,6 minutes chez le sujet âgé (65-74 ans) et de 3,6 minutes chez le sujet très âgé (75 ans ou plus). Bien que les délais de récupération chez le sujet âgé soient plus longs que dans la population adulte, aucune adaptation de doses de sugammadex n'est nécessaire dans cette population (voir rubrique 4.4). ***Patients obèses :*** Chez les patients obèses, y compris les patients présentant une obésité morbide (indice de masse corporelle ≥ 40 kg/m2), la dose de sugammadex devrait être calculée sur le poids corporel réel. Chez ces patients les doses de sugammadex recommandées sont les mêmes que pour la population adulte. ***Insuffisance hépatique :*** Aucune étude n'a été réalisée chez les patients insuffisants hépatiques. Chez les patients présentant une insuffisance hépatique sévère ou lorsque l'insuffisance hépatique s'accompagne d'une coagulopathie, des précautions doivent être prises lorsque l'utilisation du sugammadex est envisagée (voir rubrique 4.4). Insuffisance hépatique légère à modérée : le sugammadex étant principalement éliminé par voie rénale, aucune adaptation de dose n'est nécessaire. ***Population pédiatrique*** Les données relatives à la population pédiatrique sont limitées (une seule étude concernant uniquement la décurarisation suite à un bloc induit par le rocuronium, après réapparition de T_2). *Enfants et adolescents :* Pour une décurarisation en routine du bloc neuromusculaire induit par le rocuronium lors de la réapparition de T_2 chez l'enfant et l'adolescent (2-17 ans), la dose de sugammadex recommandée est de 2 mg/kg. Bridion 100 mg/ml peut être dilué à 10 mg/ml pour une plus grande précision de la dose administrée dans la population pédiatrique (voir rubrique 6.6). Les autres situations de décurarisation en routine n'ont pas été étudiées et, par conséquent, le sugammadex n'est pas recommandé dans ces situations en l'absence de données supplémentaires disponibles. La décurarisation immédiate chez l'enfant et l'adolescent n'a pas été étudiée et n'est par conséquent pas recommandée en l'absence de données complémentaires disponibles. *Nouveau-nés à terme et nourrissons :* Les données sur l'utilisation du sugammadex chez le nourrisson (30 jours à 2 ans) sont limitées ; son utilisation chez le nouveau-né à terme (moins de 30 jours) n'a pas été étudiée. L'utilisation du sugammadex chez les nouveau-nés à terme ainsi que chez les nourrissons n'est donc pas recommandée en l'absence de données supplémentaires disponibles. **Mode d'administration** Le sugammadex doit être administré par voie intraveineuse en bolus unique. L'injection en bolus doit être rapide, dans les 10 secondes, dans un cathéter intraveineux déjà mis en place (voir rubrique 6.6). Au cours des études cliniques, le sugammadex n'a été administré que par injection en bolus unique. **4.3 Contre-indications** Hypersensibilité à la substance active ou à l'un des excipients mentionnés à la rubrique 6.1. **4.8 Effets indésirables** ***Résumé du profil de tolérance*** Bridion est co-administré avec des curares et des anesthésiques chez les patients opérés. Le lien de causalité des événements indésirables est donc difficile à évaluer. Les effets indésirables les plus fréquemment rapportés chez les patients opérés étaient la toux, les complications des voies respiratoires liées à l'anesthésie, les complications anesthésiques, l'hypotension liée aux procédures et les complications liées aux procédures (fréquent (≥ 1/100, < 1/10)). ***Tableau 2 : Tableau de synthèse des effets indésirables*** La tolérance du sugammadex a été évaluée chez 3519 sujets uniques à partir d'une base de données de tolérance regroupant les études de phase I - III. Les effets indésirables suivants ont été rapportés dans les essais contrôlés *versus* placebo, chez les sujets recevant des anesthésiques et/ou des curares (1 078 sujets ayant reçu du sugammadex *versus* 544 ayant reçu du placebo) : [Très fréquent (≥ 1/10), fréquent (≥ 1/100, < 1/10), peu fréquent (≥ 1/1 000, < 1/100), rare (≥ 1/10 000, < 1/1 000), très rare (< 1/10 000)]. Classes de systèmes d'organes/Fréquences/Effets indésirables (Termes préférentiels) : Affections du système immunitaire Peu fréquent : Réactions d'hypersensibilité au médicament (voir rubrique 4.4). Affections respiratoires, thoraciques et médiastinales Fréquent : Toux. Lésions, intoxications et complications liées aux procédures Fréquent : Complication des voies respiratoires liée à l'anesthésie, Complication anesthésique (voir rubrique 4.4), Hypotension liée aux procédures, Complication liée aux procédures. ***Description de certains effets indésirables*** Réactions d'hypersensibilité au médicament : Des réactions d'hypersensibilité, incluant l'anaphylaxie, se sont produites chez certains patients et volontaires (pour des informations sur les volontaires, voir le paragraphe ci-dessous «Information sur les volontaires sains»). Au cours des essais cliniques réalisés chez les patients opérés, ces réactions ont été peu fréquemment rapportées et pour les rapports post-commercialisation, la fréquence est inconnue. Ces réactions variaient de réactions cutanées isolées à des réactions systémiques graves (c'est-à-dire anaphylaxie, choc anaphylactique) et se sont produites chez des patients sans exposition préalable au sugammadex. Les symptômes associés à ces réactions peuvent inclure : bouffées de chaleur, urticaire, rash érythémateux, hypotension (sévère), tachycardie, gonflement de la langue, gonflement du pharynx, bronchospasme et événements pulmonaires obstructifs. Les réactions sévères d'hypersensibilité peuvent être fatales. Complication des voies respiratoires liée à l'anesthésie : Les complications des voies respiratoires liées à l'anesthésie incluaient un « bucking » contre la sonde endotrachéale, une toux, un « bucking » modéré, une réaction d'éveil pendant la chirurgie, une toux au cours de la procédure d'anesthésie ou pendant la chirurgie, ou une respiration spontanée du patient liée à la procédure d'anesthésie. Complication anesthésique : Il s'agit d'une restauration de la fonction neuromusculaire, comportant des mouvements d'un membre ou du corps ou une toux pendant l'anesthésie ou la chirurgie, des grimaces ou la succion de la sonde endotrachéale. Voir rubrique 4.4 Anesthésie légère. Complication liée aux procédures : Les complications liées aux procédures incluaient la toux, la tachycardie, la bradycardie, les mouvements, et l'augmentation de la fréquence cardiaque. Bradycardie marquée : Depuis la commercialisation, des cas isolés de bradycardie marquée et de bradycardie avec arrêt cardiaque ont été observés dans les minutes suivant l'administration du sugammadex (voir rubrique 4.4). Récurrence du bloc neuromusculaire : Dans des études cliniques chez des sujets traités par le rocuronium ou le vécuronium, lorsque le sugammadex était administré à la dose recommandée selon la profondeur du bloc neuromusculaire (N = 2 022), une incidence de 0,20 % a été observée pour la récurrence du bloc neuromusculaire, sur la base d'un monitorage neuromusculaire ou de signes cliniques (voir rubrique 4.4). Information sur les volontaires sains : Une étude randomisée en double aveugle a évalué l'incidence des réactions d'hypersensibilité au médicament chez des volontaires sains recevant jusqu'à 3 doses, de placebo (N = 76), de sugammadex 4 mg/kg (N = 151) ou de sugammadex 16 mg/kg (N = 148). Les cas rapportés d'hypersensibilité suspectée ont été jugés en aveugle par un comité. L'incidence de l'hypersensibilité avérée était respectivement de 1,3%, 6,6% et 9,5% dans les groupes placebo, sugammadex 4 mg/kg et sugammadex 16 mg/kg. Il n'y a pas eu de cas d'anaphylaxie après placebo ou sugammadex 4 mg/kg. Il y a eu un seul cas d'anaphylaxie avérée après la première dose de sugammadex 16 mg/kg (incidence 0,7%). L'augmentation de la fréquence ou de la gravité de l'hypersensibilité avec des doses répétées de sugammadex n'a pas été démontrée. Dans une précédente étude avec le même design, il y a eu trois cas d'anaphylaxie avérée, tous avec sugammadex 16 mg/kg (incidence 2,0%). Dans la base de données regroupant les études de Phase I, les effets indésirables considérés comme fréquents (≥ 1/100 à < 1/10) ou très fréquents (≥ 1/10) et plus fréquents chez les sujets traités par sugammadex que ceux du groupe placebo, comprennent dysgueusie (10,1%) , céphalées (6,7%), nausées (5,6%), urticaire (1,7%), prurit (1,7%), vertiges (1,6%), vomissements (1,2%) et douleurs abdominales (1,0%). ***Informations complémentaires concernant des populations particulières*** **Patients ayant une pathologie pulmonaire :** Dans les données recueillies depuis la commercialisation et dans un essai clinique concernant des patients présentant des antécédents de complications pulmonaires, un bronchospasme a été rapporté comme évènement indésirable possiblement lié. Comme avec tous les patients avec des antécédents de complications pulmonaires, le médecin doit être averti de la survenue possible d'un bronchospasme. **Population pédiatrique** Selon une base de données limitée, le profil de tolérance du sugammadex (jusqu'à 4 mg/kg) chez les patients pédiatriques est comparable à celui observé chez l'adulte. **Patients présentant une obésité morbide** Dans un essai clinique spécifiquement mené chez des patients présentant une obésité morbide, le profil de tolérance d'effet indésirable était généralement similaire à celui observé chez l'adulte dans les études poolées de Phase I à III (voir Tableau 2). ***Déclaration des effets indésirables suspectés*** La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration: **en Belgique** : Agence Fédérale des Médicaments et des Produits de Santé - Division Vigilance, Boîte Postale 97, B-1000 Bruxelles Madou. Site internet: www.afmps.be, e-mail: adversedrugreactions@fagg-afmps.be, **au Luxembourg** : Centre Régional de Pharmacovigilance de Nancy - Bâtiment de Biologie Moléculaire et de Biopathologie (BBB) - CHRU de Nancy – Hôpitaux de Brabois, Rue du Morvan 54, 511 VANDOEUVRE LES NANCY CEDEX, Tél : (+33) 3 83 65 60 85 / 87, Fax : (+33) 3 83 65 61 33, E-mail : crpv@chru-nancy.fr ou Direction de la Santé – Division de la Pharmacie et des Médicaments, Allée Marconi - Villa Louvigny. L-2120 Luxembourg, Tél. : (+352) 2478 5592, Fax : (+352) 2479 5615, E-mail : pharmacovigilance@ms.etat.lu. Lien pour le formulaire http://www.sante.public.lu/fr/politique-sante/ministere-sante/direction-sante/div-pharmacie-medicaments/index.html. **7. TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHE** Merck Sharp & Dohme B.V., Waarderweg 39, 2031 BN Haarlem, Pays-Bas **8. NUMERO(S) D'AUTORISATION DE MISE SUR LE MARCHE** EU/1/08/466/001; EU/1/08/466/002. **9. DATE DE PREMIERE AUTORISATION/DE RENOUVELLEMENT DE L'AUTORISATION** Date de première autorisation : 25 juillet 2008. Date du dernier renouvellement : 21 juin 2013. **10. DATE DE MISE A JOUR DU TEXTE** 04/2020. **Statut légal de délivrance**: usage hospitalier. Des informations détaillées sur ce médicament sont disponibles sur le site internet de l'Agence européenne des médicaments http://www.ema.europa.eu.

(Acta Anaesth. Belg., 2020, 71, 137-140)

Anticholinergic symptoms in a patient with a bupropion overdose successfully managed with physostigmine: a case report

A.F. Kalmar (*), I. Plaetinck (*,**), J. Heerman (*), S. Van De Velde (*), S. Allaert (*)

Abstract : We report the case of anticholinergic poisoning in a patient suffering from an overdose of bupropion. The patient presented with bilateral mydriasis, involuntary movements and signs of agitation. Bupropion is commonly used as antidepressant and smoking cessation aid. It inhibits neuronal reuptake of dopamine and norepinephrine and also antagonizes acetylcholine at the level of the nicotinic receptor sites. So far bupropion overdose resulting in symptoms mimicking an anticholinergic syndrome has rarely been reported in literature.
In this case, one milligram of intravenous physostigmine, an acetylcholinesterase inhibitor, rapidly resolved patient agitation and mydriasis. This case indicates that physostigmine might be used as an antidote to quickly reverse the central and peripheral anticholinergic symptoms in patients with an overdose of bupropion.

Key words : anticholinergic symptoms ; bupropion overdose ; physostigmine.

Bupropion hydrochloride is an atypical antidepressant, also used as a smoking cessation aid. It is an antagonist of the nicotinic receptors of the autonomic ganglia and the central nervous system (). Current management of bupropion overdose is mainly supportive ; no specific antidote is available. Physostigmine is a short-acting acetylcholinesterase inhibitor that can pass freely into the central nervous system (CNS) and reverse both central and peripheral anticholinergic effects ().

Case Report

A 58-year old woman was admitted to the Intensive Care Unit (ICU) from the emergency department. The initial prehospital assessment revealed hypoxia (SpO_2 of 60% without supplemental oxygen), unconsciousness (Glasgow Coma Scale (GCS) 3/15) and mydriatic and non-reactive to light pupils. Following rapid sequence intravenous (IV) induction with 100mg rocuronium, 100µg fentanyl and 200mg ketamine, the trachea was intubated and ventilation was initiated. Because she was found alone at home, no further information was available.

On admission, blood pressure was 141/74 mmHg, heart rate 74/min, body temperature 31.2°C, glucose level 89mg/dl. Pulse oximetry during PRVC-ventilation with 100% FiO_2 was 100%. Brain-CT scan was normal. Chest-CT scan showed a pneumonic infiltrate. Lab results showed : hemoglobin 11.8g/dl (normal range 12-16g/dl), C-reactive protein 6.75mg/l (normal range 0-10 mg/dl) and white blood count 9.6. 10^3 mm^{-3}(normal range 4-10 10^3 mm^{-3}). The serum creatinine level of 1.8 mg/dl (normal range 0.7-1.3 mg/dl) suggested an acute kidney injury. Electrolytes were normal. Carbon monoxide was 0.1%. Ethanol- and paracetamol levels were low. Other toxicological screening were ongoing. The first arterial blood gas analysis (while intubated and ventilated) showed a combined metabolic and respiratory acidosis with a pH of 7.25 (normal pH 7.38-7.44), a $PaCO_2$ of 50mmHg (normal range 35-45 mmHg), a PaO_2 of 127mmHg (normal range 80-100 mmHg), lactate at 17mg/dl (normal range 6-16 mg/dl), HCO_3^- at 22mmol/l (normal range 23-28 mmol/l) and a base excess of - 5.6 mEq/l (normal range –2 - +2 mEq/l).

The initial therapy for hypothermia was the administration of 500ml of warm fluid and the use of an external heating with a forced-air patient warming device. Hypotension was treated with norepinephrine (0.15µg/kg/min). Empirical antibiotic therapy (amoxicillin-clavulanic acid

Alain Frederic Kalmar, MD; Ineke Plaetinck, MD; Jan Heerman, MD; Stijn Van De Velde, MD; Silvie Allaert, MD
(*) Department of Anesthesia and Intensive Care Medicine, Maria Middelares Hospital, Ghent, Belgium
(**) Emergency Department, Brussels University Hospital, Brussels, Belgium
Corresponding author: Alain Frederic Kalmar, MD, Maria Middelares Ziekenhuis Gent, Oost-Vlaanderen, Belgium.
Email: alainkalmar@gmail.com

Paper submitted on December 5, 2019 and accepted on October 15, 2020
Conflict of interest: This study was solely supported by departmental and institutional funding.

with clarithromycin) was given for the pulmonary infection. The patient was transferred to the ICU with a probable diagnosis of septic shock and encephalopathy based on a pulmonary infection. A central nervous system infection or intoxication could not be excluded.

On ICU admission, the body temperature was still 31.2°C despite external warming. GCS was still at 3/15. Residual neuromuscular blockade was suspected despite a 180-minute delay after administration of rocuronium. Complete recovery of motor response was achieved quickly after administration of sugammadex. This prolonged effect can be mainly attributed to hypothermia. () However, the patient was very agitated and had non-reactive mydriasis. As prolonged ventilation was required due to hypoxia, sedation with propofol and remifentanil was initiated.

Thirty-six hours after admission, involuntary movements persisted, and the pupils remained dilated and unresponsive to light. Epileptic activity was excluded by EEG.

We were then informed of her usual medication consisting of bupropion 150mg 1dd, ezetimide 10mg 1dd, amlodipine 10mg 1dd, levothyroxin 50µg 1dd and alprazolam 0.25mg if needed. We also learned that she had formulated suicidal tendencies to a friend. The level of bupropion in the blood sample taken on admission to the hospital was found to be very high with a value of 1077 ng / ml (therapeutic level <100 ng / ml).The level of the active metabolite hydroxybupropion was 6932 ng/ml (therapeutic level <1500 ng/ml). Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. The elimination half-life of 20-30 hours can take up to 60 hours, or longer in case of renal impairment (). Other tested molecules were absent or within therapeutic range (table 1).

Forty-two hours after admission, the patient was still unconscious with non-purposeful movements. The exact etiology of her condition was unclear, but there was no evidence of intracranial pathology, and she had been exposed to several neuroactive substances. The main alternative causes of coma having been excluded, a test dose of 1 mg of physostigmine was administered based on the personal experience of the treating clinician. Physostigmine had previously given positive results in comparable clinical cases. Physostigmine is a short-acting acetylcholinesterase inhibitor, described to reverse delirium from acute antimuscarinic toxicity through increasing synaptic acetylcholine([2]). Within 10-15 minutes after administration, the patient woke up, was adequate, and no longer agitated. She was extubated. Pupils returned to normal.

Table 1.

Blood level and therapeutic range of tested drugs at the moment of hospital admission

Agent	Level (ng/ml)	Therapeutic range (ng/ml)
Bupropion	1077	10-100
Hydroxybupropion	6932	850-1500
Diazepam	3.8	125-250
Desmethyl diazepam	25.8	200-800
Alprazolam	31	10-80
Tricyclic antidepressants*	negative	
Duloxetine	57	30-120

* Tricyclic antidepressants screened were amitriptyline, clomipramine, desipramine, doxepine, dosulepine, imipramine, nortriptyline, protriptyline, trimipramine.

The next day, she remained adequate.She was able to tell her story and confirmed theintentional overdose. None of the described adverse side effects of physostigmine, such as bradycardia, seizures, or respiratory distress, were observed ().

After three more days to recover from the pneumonia, the patient was transferred to the ward. The neurological recovery was uneventful. The patient did not report any explicit reminder of the period of agitation and confusion.

Discussion

This case demonstrates that physostigmine, conventionally used to treat overdose of muscarinic agonists, was very effective in reversing the symptoms of bupropion overdose.

However, in this case, many symptoms typical of bupropion overdose () were absent during the observation period. This may be because the patient was already sedated and intubated at the the time of hospitalization.

The clinical anticholinergic symptoms are mostly described with tricyclic antidepressants, antipsychotics and antihistamines (). It is a manifestation of competitive antagonism of acetylcholine at peripheral and central muscarinic receptors (). The peripheral anticholinergic symptoms include dry mouth, blurred vision and photophobia, due to dilated pupils. The skin may be warm and dry, and patients may present a paralytic ileus and urinary retention. The central anticholinergic overactivity most commonly shows agitation that may progress to a hyperactive (agitated) delirium, often with incoherent speech, and hallucinations.

Bupropion, however, is considered to have, for all practical purposes, no antimuscarinic activity (). As such, the clinically observed – both central and peripheral – anticholinergic symptoms must have resulted from its antinicotinic effects. Bupropion interferes with the ganglion-type and CNS-type nicotinic receptors ()

In this case, we predominantly observed mydriasis and hyperactive agitation as anticholinergic symptoms. In addition, the symptoms were most probably not provoked by interaction with muscarinic receptors. It is therefore remarkable that although there was no actual anticholinergic syndrome, there was a dramatic improvement after the administration of 1mg physostigmine through antagonism ofnicotinic receptors.

There is no known specific antidote for bupropion overdose. Management of bupropion overdose is mainly supportive. In one case report of a mixed overdose of bupropion and diphenhydramine (a H_1-antihistaminicum with anticholinergic activity), physostigmine also successfully resolved the hallucinations and antimuscarinic symptoms.

Unexpectedly, we noticed a reversal in our patient's clinical presentation with a single 1mg dose of physostigmine.

Physostigmine has a half-life of 1 to 2 hours, or even shorter, while bupropion and its metabolites can take up to 60 hours. Repeated administration would therefore be necessary. (11,)

This impressive difference in the half-life of physostigmine versus the course of symptoms reversal over time indicates that the beneficial effect of physostigmine cannot be attributed purely to an isolated pharmacological antagonist effect of bupropion at the level of the acetylcholine receptor. Nevertheless, this single dose was clearly sufficient to reverse the symptoms. Based on our observations, we can only speculate on the mechanism of this lasting reversal. However, a retrospective analysis of comparable cases also described that a minority of cases (12%) did not relapse after an initial dose of physostigmine for the treatment of anticholinergic poisoning (the mean initial dose was 2.2mg) ; only 58% of patients received multiple doses or continuous infusion (). It appears that in these cases, as well as in our case, an aberrant feedback mechanism in the brain was interrupted by physostigmine, leading to lasting benefits.

The ability of bupropion to interact with specific nicotine receptor subtypes has been studied using various cell expression systems. Inhibition of these nicotine receptor subtypes by bupropion is not is not overcome by increased agonist concentrations, indicative of a non-competitive mechanism of action.() In addition, physostigmine is an acetylcholinesterase inhibitor classically administered for muscarinergic intoxication. Although in this patient, there was nicotine agonist poisoning, the symptoms were typically muscaric. Despite bupropion lacks direct antimuscarinic affinity and exhibits a uncompetitive antagonism, the observation that increased acetylcholine levels resolve anticholinergic symptoms indicates that the mechanism of action of physostigmine must be more complex than the effects on a single receptor.

It is known that bupropion rarely exhibits anticholinergic effects, except when combined with other psychoactive drugs.() The observed clinical effect of physostigmine is therefore probably explained by the cessation of the delirium caused by overdose of bupropion. Despite the clear and rapid resolution of clinical symptoms, the exact mechanism by which physostigmine reversed the symptoms remains to be elucidated. Furthermore, it is interesting to wonder about the effect that physostigmine would have had on the evolution of symptoms if it had been administered (much) earlier.

It is iomportant to note that ketamine, which is thought to bind to muscarinic and nicotinic acetylcholine receptors, has been used for the induction of anesthesia. Anticholinergic symptoms after administration of ketamine are described () and could be successfully antagonized with physostigmine (). Although ketamine is a short-acting drug, an influence of ketamine on the long-lasting anticholinergic state of the patient by a strengthening effect on the anticholinergic action of bupropion cannot be excluded.

Likewise, fentanyl is reported to induce serotoninergic toxicity in rare cases, althought it is widely used. These cases are, however, always associated with much higher (often maintenance) doses of fentanyl and in the context of polypharmacy with other serotonergic agents, such as SSRIs (). While the contribution of fentanyl, if any, is probably low, we cannot exclude that fentanyl is a contributing factor in the symptoms observed.

The significantly increased levels of bupropion and hydroxybupropion, in the absence of markedly increased levels of other drugs tested, suggest a strong likelihood that symptoms at the time of admission were primarily due to isolated bupropion intoxication. Other -drugs not detected may have been involved in this poisoning. Therefore, it may be premature to assert a cause and effect relationship based on this single case. Second, caution is

advised when administering physostigmine to treat bupropion overdose, as there is often no peripheral anticholinergic effects to counter potential cholinergic agonist effects.

Conclusion

We report an unusual case of bupropion poisoning in which therapy consisting of the administration of physostigmine to reverse the effects of bupropion at the central nicotinic receptors and possibly muscarinic receptors was successful. This case strongly indicates that 1mg of physostigmine, a cholinesterase inhibitor,resulted in a complete reversal of the anticholinergic symptoms within 10-15 minutes.

References

1. Slemmer J.E., Martin B.R. and Damaj M.I. 2000. Bupropion is a nicotinic antagonist. J. Pharmacol. Exp. Ther. 295: 321-327.
2. Arens A.M. and Kearney T., Adverse Effects of Physostigmine. 2019. J. Med. Toxicol. 15: 184-191.
3. Warr J., Thiboutot Z., Rose L., Mehta S. and Burry L.D. 2011. Current Therapeutic Uses, Pharmacology, and Clinical Considerations of Neuromuscular Blocking Agents for Critically Ill Adults. Ann. Pharmacother. 45:1116-1126.
4. www.drugs.com/ppa/bupropion.html. Accessed 01 May 2020
5. Nguyen T.T., Armengol C., Wilhoite G., Cumpston K.L. and Wills B.K. 2018. Adverse events from physostigmine: An observational study. Am. J. Emerg. Med. 36:141-142.
6. Stall N., Godwin J. and Juurlink D. Bupropion abuse and overdose. CMAJ. 2014 Sep 16;186(13):1015.
7. Boley S.P., Olives T.D., Bangh S.A., Fahrner S. and Cole J.B. 2019. Physostigmine is superior to non-antidote therapy in the management of antimuscarinic delirium: a prospective study from a regional poison center. Clin. Toxicol. 57: 50-55.
8. Dawson A.H. and Buckley N.A. 2016. Pharmacological management of anticholinergic delirium – theory, evidence and practice. Br. J. Clin. Pharmacol. 81:516-524, 2016.
9. Stanton T., Bolden-Watson C., Cusack B. and Richelson E. 1993. Antagonism of the five cloned human muscarinic cholinergic receptors expressed in CHO-K1 cells by antidepressants and antihistaminics. Biochem. Pharmacol. 45: 2352-2354.
10. Rang H.P. 2003. Pharmacology. In: 5th edn. Edinburgh: Churchill Livingstone, 2003. ISBN 978-0-443-07145-4.
11. Phillips M.A., Acquisto N.M., Gorodetsky R.M. and Wiegand T.J. Use of a physostigmine continuous infusion for the treatment of severe and recurrent antimuscarinic toxicity in a mixed drug overdose. J Med Toxicol. 2014 Jun;10(2):205-9.
12. Hail S.L., Obafemi A. and Kleinschmidt K.C. Successful management of olanzapine-induced anticholinergic agitation and delirium with a continuous intravenous infusion of physostigmine in a pediatric patient. Clin Toxicol (Phila). 2013 Mar;51(3):162-6.
13. Burns M.J., Linden C.H., Graudins A., Brown R.M. and Fletcher K.E. A comparison of physostigmine and benzodiazepines for the treatment of anticholinergic poisoning, Ann Emerg Med. 2000 Apr;35(4):374-81.
14. Dwoskin L.P., Rauhut A.S. and King-Pospisil K.A., et al. Review of the pharmacology and clinical profile of bupropion, an antidepressant and tobacco use cessation agent. CNS DrgRev 2006; 12:178-207
15. Liberzon I., Dequardo J.R. and Silk K.R. Bupropion and delirium. Am J Psychiatry. 1990 Dec;147(12):1689-90.
16. Zanos P., Moaddel R., Morris P.J., Riggs L.M., Highland J.N. and Georgiou P., et al. 2018. Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. Pharmacol. Rev.. 70:621-660.
17. Mimura M., Namiki A., Kishi R., Ikeda T., Miyake H. and Iwasaki H. 1993. Central cholinergic action produces antagonism to ketamine anesthesia. M. Acta. Anaesthesiol. Scand., 36, 460-462.
18. Baldo B.A. Opioid analgesic drugs and serotonin toxicity (syndrome): mechanisms, animal models, and links to clinical effects. Arch Toxicol. 2018 Aug;92(8):2457-2473.

(Acta Anaesth. Belg., 2020, 71, 141-143)

Robinow Syndrome : an anesthetic challenge and review of literature

V. Depal (*), N. Patel (*), A. Singh (*), A. Kumar (**)

Abstract : Robinow Syndrome is characterized by the presence of mesomelic limb shortening, midfacial hypoplasia, hemivertebrae and genital hypoplasia. Multi-organ involvement including cardiac, renal, vertebral dysfunctions have been described.We here report successful anaesthetic management of 1year old boy posted for ophthalmic procedure.

Key words : Robinow syndrome ; pediatric anesthesia ; mid facial hypoplasia ; facial dysmophism ; ophthalmic surgery.

Introduction

Robinow Syndrome or Fetal Face Syndrome characterized by the presence of mesomelic limb shortening, midfacial hypoplasia hemivertebrae, and genital hypoplasia was first defined by Robinow Meinhard in 1969 (1, 2). Multi-organ involvement including cardiac, renal, vertebral dysfunctions, has also been described.

We present the case of a 1-year-old male child, a diagnosed case of Robinow Syndrome who was scheduled for an ophthalmic examination under general anesthesia and review the perioperative anesthetic concerns.

Case report

A one-year-old male child, weighing 7.5kg, born out of non-consanguineous marriage, was scheduled for ophthalmic examination under general anesthesia. He was a diagnosed case of Robinow Syndrome and presented with the classical limb shortening, hypertelorism, midfacial hypoplasia along with retrognathia, micrognathia, long philtrum, upturned nose, frontal bossing and large anterior fontanelle (Fig. 1A & B). His preoperative laboratory investigations and echocardiography were within normal limits.

After obtaining informed written consent, anesthesia was induced with 8% sevoflurane in 100 % oxygen while maintaining spontaneous respiration. A two-hand technique was used to achieve an adequate seal due to dysmorphic facial features. After achieving adequate of anesthesia, a 24G intravenous cannula was cannulated followed by Inj. Fentanyl 1µg/kg. An AMBU-LMA, size 1.0 was successfully inserted, and adequate depth of anesthesia was maintained with pressure support ventilation and Sevoflurane (Fig. 1C). The post-operative period was un-eventful. After completion, the AMBU LMA was successfully removed and the postoperative recovery was unremarkable.

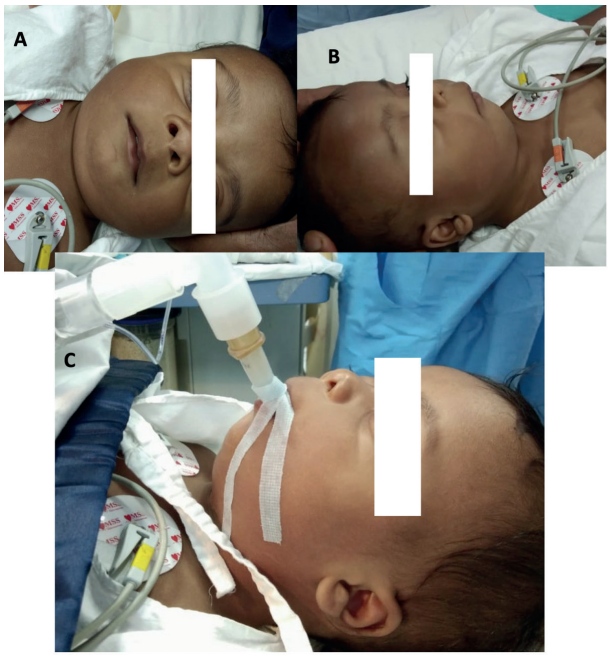

Figure 1. — A-Showing mid facial hypoplasia. B- Lateral view of face showing retrognathia and micrognathia. C-Showing successful LMA placement.

Vini Depal, MD ; Nishant Patel, MD ; Abhishek Singh, MD ; Anil Kumar, MD
(*) All India Institute of Medical Sciences New Delhi, New Delhi, India.
(**) Department of Anaesthesia Lady Hardinge Medical College, New Delhi, India.
Corresponding author : Nishant Patel, All India Institute of Medical Sciences New Delhi, New Delhi, India.
E-mail : pateldrnishant@gmail.com

Paper submitted on April 28, 2020 and accepted on July 1, 2020
Conflict of interest : None

Discussion

Robinow syndrome is a rare genetically inherited disorder. The incidence of Robinow syndrome is about 1:500,000 but prevalence is slightly lower as 5-10% of children die in infancy. The male to female ratio of Robinow syndrome is 1:1 (18). The syndrome is described in two forms, an autosomal recessive type with distinctive shortening of limbs, short stature, facial dysmorphism, and a milder autosomal dominant type with less severe abnormalities. The mutation in the ROR2 gene is responsible for the autosomal recessive type. Afzal et al. mapped the gene encoding receptor orphan receptor tyrosine kinase 2 (ROR2) to chromosome 9q22 (3, 4). Mutations in WNT5A, locus 3p14.3 (OMIM 164975) are responsible for the autosomal dominant (AD) form of RS. In these patients, oral manifestations are more prominent, hemivertebrae and scoliosis rarely occur and facial abnormalities tend to be milder.

Airway

Robinow Syndrome presents with characteristic facial dysmorphism that includes midfacial hypoplasia, hypertelorism, upturned nose, long philtrum, pseudo-exophthalmos due to lower eyelid deficiency (1,2). There is gingival hypertrophy with dental crowding. Choanal atresia (5), with cleft- lip, and palate (6) may also be observed. These features can lead to upper airway obstruction and difficulty in securing the airway (7). In our case, difficulty in the bag and mask ventilation were encountered, although the insertion of AMBU LMA was uneventful. A difficult airway cart should always be made available. Successful intubations have been reported by MacDonald et al and Lirk et al. (8, 9). However, a case report published by Weksler et al described difficult laryngoscopy and unsuccessful tracheal intubation in a case of Robinow Syndrome, nevertheless, they were able to use LMA as a rescue device to secure airway (10). Cassinello Ogea C et al also reported the successful use of LMA in a case of Robinow Syndrome with difficult airway and grade IV Cormack-Lehane (11).

Skeletal abnormalities

These patients may present with hemivertebrae leading to kyphoscoliosis, fused, or missing ribs leading to chest deformity (6). This may affect respiratory function and pulmonary gas exchange (9). Vertebral anomalies may prove a hindrance to regional anesthesia, and therefore should be evaluated beforehand.

MacDonald and Dearlove reported the use of a single-shot caudal block in a patient posted for psoas hitch procedure successfully. Except for increased sacral dimpling, the spine and pelvis were otherwise normal (8).

Cardiac Anomalies

A major concern for the anesthesiologists is the presence of congenital heart disease.

Patton reported pulmonary stenosis or atresia as the most common defect, followed by septal defects, coarctation of the aorta, tricuspid atresia, and tetralogy of Fallot (6, 12). The patient should be screened to rule out congenital heart disease and preoperative echocardiography should be done in patients with definite symptoms.

Renal and Genitourinary anomalies

Genital hypoplasia in terms of the hypoplastic clitoris and labia minora/Majora in females or a small penis with a normal scrotum and testis in males have been observed (13). Obstructive uropathy, renal cysts, hydronephrosis are other anomalies

Table I

Various organ system involvement and anesthetic implications in a patient with Robinow Syndrome

Organ involvement	Characteristic finding	Anesthetic implication
Airway	Midfacial Hypoplasia, retrognathia, micrognathia, choanal atresia, cleft lip and cleft palate, gingival hyperpalsia	Difficult airway, bag mask ventilation and intubation
Cardiovascular	Pulmonary stenosis, septal defects, coarctation of aorta, tricuspid atresia, Tetralogy of Fallots	Anesthetic implication as per cardiac lesion
Vertebral and Skeletal abnormalities	Mesomelic limb shortening, hemivertebrae, kyphoscoliosis, fused ribs	Difficulty in positioning, difficulty in giving regional block, respiratory complication
Genito-urinary	Genital hypoplasia, obstructive uropathy, renal cysts, hydronephrosis	Renal failure, drug dose modification
Eye	Pseudo-exophthalmos	Proper protection is needed
Central nervous system	Mental retardation, developmental delay	Judicious use of anaesthetic drugs
Liver	Association with Criggler-Najjar Syndrome	Proper evaluation of liver function is needed

(14). A preliminary renal function should be done to look for any derangement and further evaluation should include ultrasonography.

Central Nervous System

Intelligence is usually normal but mental retardation and developmental delay have been noted in up to 20 % of patients with Robinow syndrome (6).

Endocrinology

In male patients, low testosterone levels and impaired testosterone response to human chorionic gonadotropin stimulation are seen ; whereas in female patients, the hypothalamic-pituitary axis or the hormonal response of the ovaries seems to be impaired (15).

Hepatic abnormalities

An association with Crigler-Najjar has been reported in the literature, although not proven. A baseline liver function should be done to rule out any abnormality (16, 17).

Conclusion

A patient with Robinow Syndrome may prove as a challenge to the anesthesiologists due to difficult airway and the high incidence of congenital heart disease. A thorough physical examination and history along with necessary investigations preoperatively with proper preparation for difficult airway can help improve the outcome in these patients.

Reference

1. Robinow M., Silverman F. N., & Smith H. D. 1969. A newly recognized dwarfing syndrome. *American journal of diseases of children*, 117(6):645-651.
2. Robinow M. 1993. The Robinow (foetal face) syndrome : a continuing puzzle. *Clinical dysmorphology*, *2*(3), 189-198.
3. Afzal A. R., Rajab A., Fenske C., Crosby A., Lahiri N., Ternes-Pereira E., ... & Jeffery S. 2000. Linkage of recessive Robinow syndrome to a 4ácM interval on chromosome 9q22. *Human genetics*, 106(3):351-354.
4. Van Bokhoven H., Celli J., Kayserili H., van Beusekom E., Balci S., Brussel W., & Brunner H. G. 2000. Mutation of the gene encoding the ROR2 tyrosine kinase causes autosomal recessive Robinow syndrome. *Nature genetics*, 25(4):423-426.
5. Hacer Y., Murat B., Aydin F., Sitki N. S., Kerem E. and Ayşin S.2017.Anesthesia management in Robinow syndrome (a case report). *Bagcilar Medical Bulletin*, 2(1):36-38.
6. Patton M. A., & Afzal A. R. 2002. Robinow syndrome. *Journal of medical genetics*, 39(5):305-310.
7. Butler M. G., Hayes B. G., Hathaway M. M., & Begleiter M. L. 2000. Specific genetic diseases at risk for sedation/anaesthesia complications. *Anesthesia and analgesia*, 91(4): 837.
8. Macdonald, I., & Dearlove O. R. 1995. Anaesthesia and Robinow syndrome. *Anaesthesia*, 50(12):1097-1097.
9. Lirk, P., Rieder J., Schuerholz A., & Keller C. 2003. Anaesthetic implications of Robinow syndrome. *Pediatric Anesthesia*, 13(8):725-727.
10. Weksler N., Schwartz A., Klein M., Rozentsveig V., Weksler D., & Gurman G. M. 2006. Laryngeal mask airway and the Robinow syndrome. *Minerva anestesiologica*, 72(1-2):81-83.
11. Cassinello C. O., Gil L. B., Oliva P. P., Casado A. M., Izquierdo B. V., & Fernández J. L. 2003. Anaesthesia and fibro bronchoscopy for the study of chronic stridor in a boy with Robinow syndrome. *Revista espanola de anestesiologia y reanimacion*, 50(2):101-105.
12. Webber S. A., Wargowski D. S., Chitayat D., & Sando, G. G. 1990. Congenital heart disease and Robinow syndrome : coincidence or an additional component of the syndrome?. *American journal of medical genetics*, 37(4): 519-521.
13. Lee P. A., Danish R. K., Mazur T., & Migeon C. J. 1980. Micropenis. III. Primary hypogonadism, partial androgen insensitivity syndrome, and idiopathic disorders. *The Johns Hopkins medical journal*, 147(5):175-181.
14. Wiens L., Strickland D. K., Sniffen B., & Warady B. A. 1990. Robinow syndrome : report of two patients with cystic kidney disease. *Clinical genetics*, 37(6):481-484.
15. Soliman A. T., Rajab A., Alsalmi I., & Bedair S. M. A. 1998. Recessive Robinow syndrome: with emphasis on endocrine functions. *Metabolism*, 47(11):1337-1343.
16. Nazer H., Gunasekara, T. S., Sakati N. A., & Nyhan W. L. 1990. Concurrence of robinow syndrome and Crigler-Najar syndrome in two offspring of first cousins. *American journal of medical genetics*, 37(4):516-518.
17. Sleesman J. B., & Tobias J. D. 2003. Anaesthetic implications of the child with Robinow syndrome. *Pediatric Anaesthesia*, 13(7):629-632.
18. Hosalkar, H. S., Gerardi, J., & Shaw, B. A. 2002. Robinow syndrome. *Journal of postgraduate medicine*, 48(1):50.

(Acta Anaesth. Belg., 2020, 71, 145-150)

Regional anesthesia combined with virtual reality hypnosis for extended orthopedic surgery: two case reports

L. De Schrijver (*), L.A. Sermeus (*,**), S. Maes (*), H. Camerlynck (*), S. Morrison (*)

Abstract : *Background :* Virtual reality hypnosis is a combination of visual immersion in a virtual reality environment and clinical hypnosis. It can be used in addition to conventional techniques, for sedation and pain management during wound care. Patients undergoing painful and long-lasting procedures under regional anesthesia could also benefit, from this technique alleviating the need for sedative-hypnotic medication.
Case presentation : Two patients with relative contra-indications for general anesthesia underwent lengthy orthopedic surgery of the upper limbs under regional anesthesia with additional virtual reality hypnosis. Written informed consent was obtained from both patients before surgery. A 69-year-old man, with a previous medical history of severe symptomatic aortic valve stenosis (ɵ 0.69cm^2, max/mean gradient of 91/58mmHg) sustained a proximal humerus fracture-dislocation and was scheduled to undergo shoulder hemi-arthroplasty. Anesthesia was provided with ultrasound-guided continuous interscalene block at the C5-C6 level (11mL levobupivacaine 0.5%) combined with a single-shot superficial cervical plexus block (6mL levobupivacaine 0.5%). The second case was a 56-year-old man suffering from rheumatoid arthritis with severe restrictive lung function due to interstitial lung disease and bilateral bronchiectasis. He received a unilateral elbow prosthesis. Continuous infra-clavicular brachial plexus block, performed under ultrasound guidance was provided (20 mL mepivacaine 1.5%). Both patients required prolonged immobilization on the operating table. We used virtual reality hypnosis to induce sedation and improve comfort without using medication. This was provided by headphones and head-mounted goggles, showing computer generated images of underwater scenes (Aqua module, Oncomfort ™). Both surgeries were uneventful during which time cardiorespiratory stability was maintained. Patients were comfortable during and satisfied after surgery. No sedative drugs were given before nor during the procedures.
Conclusion : Non-pharmacological sedation can be achieved with virtual reality hypnosis. When combined with regional anesthesia, this technique provides satisfactory sedation when pharmacological methods may be hazardous.

Key words : Virtual Reality ; hypnosis ; regional anesthesia ; pain management.

Background

The application of virtual reality (VR) for clinical purposes is not novel (1). In the past this technology was successfully applied during the care of patients with burn injuries, decreasing the need for opioids and increasing patient comfort (2). At that time the appliances required to provide VR were a lot bulkier than they are nowadays. The entertainment industry has provided us with smaller devices, making them more applicable in a clinical setting. This technique offers a feeling of immersion, the extent to which technology delivers an inclusive, extensive, surrounding and vivid illusion to the senses of anyone (3). It also provides a sense of presence which is a state of consciousness where one has the sensation of being in this VR environment. Over two decades ago, a review discussing the use of VR in anesthesia highlighted the deficiencies of the available technology for medical applications (4). VR can be used as a medium to deliver distraction, with good results for managing pain and distress during painful procedures (5-8). Patients respond favorably to this kind of distraction provided through VR, such as a controlled thermal heat stimulus given to the skin, transurethral microwave thermotherapy or burn wound care (9-11). The use of virtual reality distraction (VRD) has even been

Lennert De Schrijver, MD.; Luc A. Sermeus, MD., PhD ; Sabine Maes, MD ; H. Camerlynck, MD, Stuart Morrison, MD
(*) Department of Anesthesiology, Antwerp University Hospital, University of Antwerp, Belgium
(**) Department of Anesthesiology, Cliniques Universitaires Saint Luc, Catholic University of Louvain, Brussels, Belgium ; Former Antwerp University Hospital, University of Antwerp, Antwerp, Belgium
Corresponding author: Luc Sermeus MD, PhD, Department of Anesthesiology, Cliniques Universitaires St. Luc, Av. Hippocrate, 10, 1200 Brussels, Belgium. Tel: +32 2 764 14 18
E-mail: luc.sermeus@uclouvain.be

Paper submitted on October 30, 2019 and accepted on May 19, 2020
Conflict of interest: None

successfully demonstrated in an operating theatre during orthopedic surgery (12). The goal of exposing patients to a VR environment in a clinical setting is to manage their pain and distress. Similarly, hypnosis has been used effectively for both acute or procedural related pain, or chronic pain management, with patients experiencing a significant positive effect on pain perception and distress (13, 14). The surgical settings in which hypnosis was applied, are mostly restricted to minimal invasive surgeries such as percutaneous vascular and renal surgery, biopsies or burn wound care. Virtual reality hypnosis (VRH) is when the immersive imagery from a VR device and clinical hypnosis are combined. With this technique the induction of hypnotic analgesia is being guided by VR. The authors of this case report hypothesize that a combination could improve the results of both techniques individually. Furthermore, combined VRH has shown advantages in comparison to drug-induced sedation regarding the respiratory side effects and anesthesiologist's satisfaction (15). Limiting opioid use might reduce opioid-related adverse side effects or the potential for misuse (16). In this article, we describe two cases of prolonged orthopedic surgery in patients who had a relative contraindication for general anesthesia. Both case reports illustrate how pharmacological sedation was avoided by using VRH in combination with regional anesthesia (RA).

Case Presentations

Case 1

A 69-year-old man (BMI 26.8 kg/m^2) required a hemi-arthroplasty procedure of the left shoulder following trauma sustained during a syncopal episode. The patient had previously undergone aortic valve replacement 8 years earlier, but due to severe symptomatic restenosis of the bioprosthesis, a secondary trans-catheter aortic valve repair had been planned for the near future (ɵ 0.69cm^2, max/mean gradient of 91/58mmHg). Further medical problems included arterial hypertension and mild (GOLD grade 1) Chronic Obstructive Pulmonary Disease (COPD). His general practitioner reported mild alcoholism. On clinical inspection we observed a relative inactive patient with a metabolic equivalent score (METS) lower than three (17). His activity was limited to slow-paced walking and he didn't perform any activities of a moderate or profound intensity. A complete blood count showed a hemoglobin level of 7.8 g/dL. To improve the patient's condition, two units of packed cells were administered before surgery, which was planned nine days after the trauma. Due to his cardiac status, RA was considered the best option for the surgery. A continuous interscalene block at the C5-C6 level was performed under ultrasound guidance (P9, General Electric, USA), in combination with nerve stimulation at 0.4mA (Stimuplex, BBraun, Melsungen, Germany) and the use of an injection pressure limiter (NerveGuard, Pajunk, Geisingen, Germany). An interscalene catheter (Contiplex, BBraun, Melsungen, Germany) was placed following injection of levobupivacaine 0.5%, 11mL (Chirocaine, Abbvie, Wavre, Belgium). Additionally, a single-shot superficial cervical plexus block was performed with 6mL of levobupivacaine 0.5%. Hemodynamic monitoring was applied with pulse oximetry (SpO_2), electrocardiography (ECG) and invasive blood pressure measurement via a right radial arterial catheter. The surgical procedure lasted 90 minutes during which the patient remained hemodynamically stable. No sedative medications were used pre- or perioperatively. The postoperative period was uneventful, without the need for intensive care, and the patient was discharged four days after surgery.

Case 2

A 56-year-old man (BMI 22.8kg/m^2) with severe rheumatoid arthritis was scheduled for an elective prosthetic replacement of his painful and disabled left elbow joint. Clinical cardiac function was satisfactory (METS > 3). Preoperative assessment revealed severe restrictive lung function secondary to interstitial lung disease and bilateral bronchiectasis, most likely related to chronic use of corticosteroids. Pulmonary function testing demonstrated a FEV1/FVC ratio of 76% (Forced Expiratory Volume in 1 s / Forced Vital Capacity) a Forced Vital Capacity of 1.78L (47% of predicted value) and a Forced Expiratory Volume in 1 s of 1.36L (47% of predicted value). He reported a dyspneic feeling in rest and a marked limitation while performing physical demanding activities such as cycling or climbing the stairs. A preoperative ECG was normal. RA was considered the best anesthetic technique due to the limited pulmonary function. A continuous infraclavicular block was induced with ultrasound guidance (Sonolong, Pajunk, Geisingen, Germany) along with nerve stimulation at 0.4mA and the use of an injection pressure limiter. Twenty mL of mepivacaine 1.5% (Scandicaine, Aspen Pharma, Dublin, Ireland) was injected. Setup was comparable to the first case regarding routine monitoring. No

sedative medications were administered before or during the surgery. Monitored parameters remained stable during the entire surgery, which lasted for approximately 2 hours. The patient was discharged on the 4th day of hospitalization.

Virtual reality hypnosis

In both cases VRH with a head mounted display (HMD) and headphones was proposed as additional non-pharmacological sedation. A written informed consent from both patients was obtained during a preoperative assessment. At the time of surgery, the anesthesiologist was responsible for the set-up of the VRH device. The head-mounted goggles (Samsung Gear VR R323 by Oculus) and appropriate headphones (Sennheiser HD400s) were placed after patient positioning and preparation of the sterile field (figure 1). The VR program (Aqua Module Dutch version 4.0, Oncomfort™ SA, Wavre, Belgium) was initiated after reviewing the instructions with the patient. This program creates a simulation of diving into an undersea environment (http://www.oncomfort.com/en). In the surroundings of this VR world, the patients experience a lively illusion where they are challenged with the idea of existing in this simulation. These are principles of the feeling of immersion and the sense of presence, although this has not been validated through studies for this equipment. On top of this, clinical hypnosis is given through an audio script which gives continuous suggestions for progressive muscle relaxation, deep breathing and wellbeing. Patients are being guided into a relaxed state of heightened focus and concentration in order to alter the patient's pain experience. The patient from case 1 gave no indication of pain and scored this as a 1 out of 10 on a numeric rating scale (NRS) perioperatively. When asked, he was comfortable during surgery and confirmed his satisfaction with the use of VRH. The patient from case 2 asked if the HMD and headphones could be removed 90 minutes after the incision because the program had ended. At this point he felt he no longer needed the VR device. After removal of the headset, the pressure of the tourniquet started to cause discomfort. He reported to become more aware of the operation through movement of his arm and the loud sounds of the drilling and hammering. After recovery and rehabilitation, this patient planned to have his right elbow operated as well. When asked if he would opt for RA supplemented with VRH for the following procedure, he responded positively.

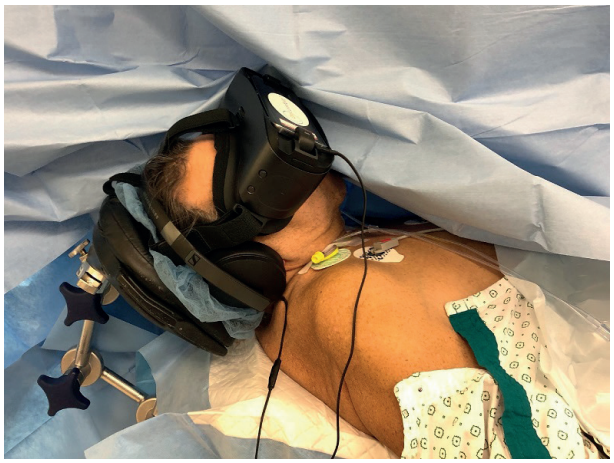

Figure 1. Setup of a patient with the virtual reality goggles and headphones behind the sterile field (case 1).

Discussion

We investigated the concept of applying a combination of virtual reality and hypnosis in a medical setting and more specifically during RA for upper limb surgery. The concept of distraction with a VR device has already been successfully investigated in a study of 9 patients that underwent orthopedic surgery of the lower limbs (12). These patients were treated with VRD that was guided by audiphones playing classical music. They did not receive hypnosis, but the results demonstrated the beneficial potential of a VR device in the setting of an operating theatre. Both patients in current case report received VRH, which is a combination of a visual immersion in a VR world while at the same time listening to a hypnotic script that induces relaxation through focused attention. Both techniques strive to achieve a similar goal which is to diminish negative and painful perceptions. It has been suggested that VR has the potential to aid hypnotic interventions by guiding someone with the visualization process (18). Patients might find comfort with an immersive visual assistance when given clinical hypnosis. Hypnosis is a beneficial technique, but there are some factors limiting widespread use. It is a one on one intervention, making it a challenge when there is limited medical personnel with sufficient hypnosis training. It is unilingual and patient and medical personnel could be prejudiced. In literature it has been documented as an alternative means for pain management (19-22). It induces dissociation between pain sensation and the emotional component of the pain experience (23). The patients pass into a hypnotic state through focused attention. Clinical hypnosis reduces involuntary movements, stabilizes vital signs and

results in reduced subjective peripheral awareness and time distortion (24). It is currently considered as a well-established treatment for acute and chronic pain (22). Enea et al. emphasized the difference between someone who is highly hypnotizable and someone who is low hypnotizable (25). To assess for a patient's hypnotizability level they used the Harvard Group Scale of Hypnotic Susceptibility, Form A. In their study it was shown that both types of persons (high and low hypnotizable) responded well to VRH. Hypnosis susceptibility was not investigated in our patients prior to surgery.

Distraction through VR (VRD) without hypnosis is an effective technique. It provides an increase in general insensibility to pain without diminishing consciousness (26). One study reported a significant decrease in the administered doses of fentanyl and midazolam when VRD was applied during preoperative perineural catheter insertion (8). Such an analgesic effect with VRD is also supported by a study of Hoffman et al (9). With the aid of functional magnetic resonance imaging and a non-ferromagnetic VR helmet, lower pain-related brain activity was observed in the regions of the insula, secondary somatosensory cortex (SS2) and thalamus during a thermal pain stimulus. These neuroanatomic regions are a part of the 'pain matrix' and become metabolically active during nociceptive stimulation when subjects report subjective pain. A combination of opioids and VRD was more effective than opioids alone or VRD alone. The authors recommend a multimodal analgesic approach. Such a strategy was used in our cases as RA is combined with VRH. More specifically, VRH itself adheres to such a multimodal approach as it combines VRD and clinical hypnosis, both independent analgesic techniques.

Our two case reports support the use of VRH with RA in the safe environment of an operating theatre where continued monitoring by well-trained medical staff and the resources for urgent intervention, if necessary, remain constantly available. The technology of Oncomfort ™ uses a HMD and separate headphones for VRH. These devices are all retrieved from a single kit which holds an instruction manual in different languages. This setup was well tolerated by the patient and the operating staff, and did not interfere with the surgery. The additional time required for installation of the VRH device was negligible, considering the anesthesiologist was experienced with the instructions. The HMD and respective phone were disinfected before and after usage to promote a sterile environment. The patient could interact with the anesthesiologist at any time during the procedure. The responsibility of providing VRH belongs to the anesthesiologist who should be aware of its functionality at all time during surgery. With a HMD however, it is difficult to assess whether the patient is asleep or engaged with the VRH. This has already been indicated by Chan et al (12). As yet it is uncertain whether integrated electro-encephalogram monitoring might aid in evaluating the depth of sedation. Our two patients demonstrated excellent cooperation with the HMD and reported to be awake during the entire length of surgery. The anesthesiologist regularly checked the positioning of this device and its activity. A single congress abstract describes the use of VR with a HMD as a preferred method by patients in comparison to standard retrieval conditions in which no devices are used (5). Another study compared VRD with video in a population of patients that received painful dental procedures (6). They noticed that there was a preference for a VR-device as opposed to a video. It should be noted that certain contra-indications are listed by Oncomfort™ : deafness or poor hearing, severe visual impairment, wounds or infections on the head, severe cognitive, behavioral or anxiety disorders, or phobia for water or sea. Our patients did not exhibit such traits.

Both patients underwent procedures under RA without receiving sedative-hypnotic medication. They remained calm and motionless, so surgery and aseptic technique were not comprised at any time. The orthopedic surgical stimulation (hammering, pneumatic drilling and prosthesis placement) did not disturb the patients while wearing the HMD. Side effects of sedative-hypnotic medications were avoided in these high-risk patients with this non-pharmacological approach. They remained hemodynamically stable and showed no signs of respiratory depression. A study by Moon et al. investigated the incidence of apnea between a group receiving VRH and a another group receiving sedation with midazolam (15). They reported a significant lower incidence of apneas in the VRH group. Sedation with intravenous midazolam is known to cause respiratory depression and patients with COPD are at high risk for this side effect (27, 28). Therefore, the possibility of such adverse drug effects was eliminated in both our cases. A recently published study has even researched the possibility of music medicine as an alternative for midazolam during the preoperative placement of nerve blocks (29). These results require further investigation but such studies demonstrate the ongoing pursuit for better non-pharmacological approaches to reduce

anxiety and improve analgesia during painful procedures.

VRH is an innocuous technology that, as an effective analgesic intervention, can be used as a cost-effective treatment. Anesthesiologists still remain diffident to this new technology, and it is not commonly proposed to patients. A reported benefit of VRH is the higher satisfaction for both the anesthesiologist and the patient (15). Careful assessment of each patient is of importance before applying VRH. An important prerequisite for success is to have a patient that is motivated to use this approach. Information regarding the application of VRH should be given during a preoperative assessment. This promotes shared decision making and allows the patient to give informed consent. Such technology can encourage patients, in particular high-risk patients, to agree to RA. They can find comfort in the combination of hypnosis and distraction during long-lasting procedures.

In conclusion, we report our experience with VRH as an effective non-pharmacological method for improving patient comfort during prolonged upper limb orthopedic surgery with RA. A principle advantage of this technique is the avoidance of sedative-hypnotic medication, which might otherwise compromise cardiorespiratory stability, especially in high risk patients. Patient comfort and satisfaction can be assured. The technique should be discussed with the patient when consent for an RA technique is being proposed. We suggest that further randomized controlled trials should be performed to investigate these encouraging findings.

Acknowledgement

Al data were collected at the Antwerp University Hospital.

References

1. Li A, Montaño Z, Chen VJ and Gold JI. 2011. Virtual reality and pain management : current trends and future directions. Pain Manag. 1:147-57.
2. Hoffman HG, Doctor JN, Patterson DR, Carrougher GJ and Furness III TA. 2000. Virtual reality as an adjunctive pain control during burn wound care in adolescent patients. Pain. 85(1):305-9.
3. Slater M and Wilbur S. 1997. A Framework for Immersive Virtual Environments (FIVE) : Speculations on the Role of Presence in Virtual Environments. Presence. 6:603-16.
4. Burt DE. 1995. Virtual reality in anaesthesia. Br J Anaesth. 75:472-80.
5. Palter SF, Sobko-Koziupa O, Gilhuly T and Pyer C. 2000. Use of a Head Mounted Display (HMD) Virtual Reality (VR) Headset as a Patient Distraction Device for Surgical Procedures Under Local Anesthesia/Sedation. Fertil Steril. 74:S203.
6. Furman E, Jasinevicius TR, Bissada NF, Victoroff KZ, Skillicorn R and Buchner M. 2009. Virtual Reality Distraction for Pain Control During Periodontal Scaling and Root Planing Procedures. J Am Dent Assoc. 140:1508-16.
7. Al-Halabi MN, Bshara N and AlNerabieah Z. 2018. Effectiveness of audio visual distraction using virtual reality eyeglasses versus tablet device in child behavioral management during inferior alveolar nerve block. Anaesth Pain & Intensive Care. 22(1):55-61.
8. Pandya PG, Kim TE, Howard SK, Stary E, Leng JC, Hunter OO and Mariano ER. 2017. Virtual reality distraction decreases routine intravenous sedation and procedure-related pain during preoperative adductor canal catheter insertion : a retrospective study. Korean J Anesth. 70:439-45.
9. Hoffman HG, Richards TL, Oostrom T Van, Coda BA, Jensen MP, Blough DK and Sharar SR. 2007. The Analgesic Effects of Opioids and Immersive Virtual Reality Distraction : Evidence from Subjective and Functional Brain Imaging Assessments. Anesth Analg. 105(6):1776-83.
10. Wright JL, Hoffman HG and Sweet RM. 2005. Virtual reality as an adjunctive pain control during transurethral microwave thermotherapy. Urology. 66:1320.e1-1320.e3.
11. Patterson DR, Wiechman SA, Jensen M and Sharar SR. 2006. Hypnosis Delivered Through Immersive Virtual Reality for Burn Pain : A Clinical Case Series. Int J Clin Exp Hypn. 54(2):130-42.
12. Chan PY and Scharf S. 2017. Virtual Reality as an Adjunctive Nonpharmacological Sedative During Orthopedic Surgery Under Regional Anesthesia : A Pilot and Feasibility Study. Anesth Analg. 125:1200-2.
13. Flory N, M Martinez Salazar G and Lang E0 2007. Hypnosis for Acute Distress Management During Medical Procedures. Int J Clin Exp Hypn. 55:303-17.
14. Stoelb BL, Molton IR, Jensen MP and Patterson DR. 2009. The efficacy of hypnotic analgesia in adults : A review of the literature. Contemp Hypn. 26:24-39.
15. Moon JY, Shin J, Chung J, Ji S-H, Ro and Kim WH. 2018. Virtual Reality Distraction during Endoscopic Urologic Surgery under Spinal Anesthesia : A Randomized Controlled Trial. J Clin Med. 20:8.
16. Koepke EJ, Manning EL, Miller TE, Ganesh A, Williams DGA and Manning MW. 2018. The rising tide of opioid use and abuse : the role of the anesthesiologist. Perioper Med. 7:16.
17. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DRJ and Tudor-Locke C, et al. 2011. Compendium of Physical Activities : a second update of codes and MET values. Med Sci Sports Exerc. 43:1575-81.
18. Thompson T, Steffert T, Steed A and Gruzelier J. 2011. A Randomized Controlled Trial of the Effects of Hypnosis With 3-D Virtual Reality Animation on Tiredness, Mood, and Salivary Cortisol. Int J Clin Exp Hypn. 59:122-42.
19. Jensen M and Patterson D. 2006. Hypnotic Treatment of Chronic Pain. J Behav Med. 29:95-124.
20. Lang E V, Berbaum KS, Faintuch S, Hatsiopoulou O, Halsey N and Li X, et al. 2006. Adjunctive self-hypnotic relaxation for outpatient medical procedures : a prospective randomized trial with women undergoing large core breast biopsy. Pain. 126:155-64.
21. Lang E V, Berbaum KS, Pauker SG, Faintuch S, Salazar GM and Lutgendorf S, et al. 2008. Beneficial effects of hypnosis and adverse effects of empathic attention during percutaneous tumor treatment : when being nice does not suffice. J Vasc Interv Radiol. 19:897-905.
22. Landry M, Lifshitz M and Raz A. 2017. Brain correlates of hypnosis : A systematic review and meta-analytic exploration. Neurosci Biobehav Rev. 81:75-98.

23. Faymonville M-E, Laureys S, Degueldre C, DelFiore G, Luxen A and Franck G, et al. Neural Mechanisms of Antinociceptive Effects of Hypnosis. Anesthesiology. 92:1257-67.
24. Vanhaudenhuyse A, Laureys S and Faymonville M-E. 2014. Neurophysiology of hypnosis. Neurophysiol Clin Neurophysiol. 44:343-53.
25. Enea V, Dafinoiu I, Opris D and David D. 2014. Effects of hypnotic analgesia and virtual reality on the reduction of experimental pain among high and low hypnotizables. Int J Clin Exp Hypn. 62:360-77.
26. Gold JI, Kant AJ, Kim SH and Rizzo A. 2005. Virtual anesthesia : The use of virtual reality for pain distraction during acute medical interventions. Semin Anesth Perioper Med Pain. 24:203-10.
27. Olkkola KT and Ahonen J. 2008. Midazolam and other benzodiazepines. Handb Exp Pharmacol. 182: 335-60.
28. Reves JG, Fragen RJ, Vinik HR and Greenblatt DJ. 1985. Midazolam : pharmacology and uses. Anesthesiology. 62:310-24.
29. Graff V, Cai L, Badiola I and Elkassabany NM. 2019. Music versus midazolam during preoperative nerve block placements : a prospective randomized controlled study. Reg Anesth & Pain Med. 44:796-99.

(Acta Anaesth. Belg., 2020, 71, 151-161)

Guidelines for the safe clinical practice of peripheral nerve blocks in the adult patient

M. Desmet (*), S. Bindelle (**), M.B. Breebaart (***), H. Camerlynck (***), S. Casaer (****), K. Fourneau (*****), P. Gautier (******), P. Goffin (**), J.P. Lecoq (*******), I. Lenders (********), I. Leunen (*********), D. Van Aken (**********), P. Van Houwe (****), S. Van Hooreweghe (***********), K. Vermeylen (*********), L. Sermeus (************)

Abstract : The Peripheral Nerve Block working group of the Belgian Association for Regional Anesthesia has revised and updated the "Clinical guidelines for the practice of peripheral nerve block in the adult" which were published in 2013.

Key words : Regional anesthesia ; peripheral nerve blocks ; guidelines.

Introduction

In 2013, the first "Clinical guidelines for the practice of peripheral nerve blocks in the adult" were published by the Belgian Association for Regional Anesthesia (BARA) Peripheral Nerve Block working group (1). Since then a plethora on research has been published providing new insights in the clinical practice of peripheral nerve blocks (PNBs). The aim of this revised version is to provide anesthesiologists an update of the 2013 guidelines according to the most recent evidence in an effort to further enhance quality and safety of clinical practice. These recommendations were composed by the BARA Peripheral Nerve Block working group which included elected BARA board members and non-board BARA all of them with an extensive experience in regional anesthesia (RA). A large-scale review of the literature regarding different topics was performed to support the guidelines by current evidence. However, in case of limited available data, expert opinion as a result of discussion within the working group, was used as a surrogate for robust data.

We would like to remind readers of this manuscript that although these guidelines are intended to optimize patient care, they do not replace sound clinical judgment and cannot ensure the avoidance of adverse outcomes. Furthermore, although great care has been taken to avoid conflict with the "Safety First Guidelines" issued by the Society for Anesthesia and Resuscitation of Belgium (SARB) and the Belgian Professional Association of Specialists in Anesthesia and Resuscitation (BSAR-APSAR), we emphasize that the "Safety First Guidelines" should be prioritized above the "Guidelines for the safe

Matthias Desmet, MD ; Simon P.F. Bindelle, MD EDRA ; Margaretha B. Breebaart, MD PhD EDRA ; Hélène Camerlynck, MD ; Sari Casaer, MD EDRA ; Kristof Fourneau, MD ; Philippe Gautier, MD ; Pierre Goffin, MD MSc ; Jean-Pierre Lecocq, MD ; Isabelle Lenders, MD ; Ine Leunen, MD ; David Van Aken, MD EDRA

(*) Dept of Anesthesia, AZ Groeninge, Belgium.

(**) Dept of Anesthesia, Clinique MontLegia, CHC Groupe Santé, Liège, Belgium.

(***) Dept of Anesthesia, Universitaire Ziekenhuizen Antwerpen, Antwerp, Belgium.

(****) Dept of Anesthesia, GZA Ziekenhuizen, Antwerp, Belgium.

(*****) Dept. of Anesthesia, AZ Alma, Eeklo, Belgium.

(******) Dept of Anesthesia, Clinique Ste Anne-St Remi, CHIREC, Brussels, Belgium.

(*******) Dept of Anesthesia, CHU Sart Tilman, Liège, Belgium.

(********) Dept of Anesthesia, UZ Leuven, Leuven, Belgium.

(*********) Dept of Anesthesia, AZ Turnhout, Turnhout, Belgium.

(**********) Dept of Anesthesia, AZ Klina, Brasschaat, Belgium.

(***********) Dept of Anesthesia, Jan Yperman Ziekenhuis, Ieper, Belgium.

(************) Dept of Anesthesia, Cliniques Universitaires Saint Luc, Brussels, Belgium.

The guidelines are endorsed by the Board of the Belgian Association for Regional Anesthesia (BARA) : Margaretha Breebaart MB, Casaer S, Coppens S, Desmet M, Dewandre PY, Gautier P, Guntz E, Leunen I, Roofthooft E, Sermeus L, Van de Velde M, Vermeylen K.

The guidelines are endorsed by the Society for Anesthesia and Resuscitation of Belgium (SARB) : Bonhomme V, Wouters P, Foubert L, Van de Velde M, Brichant JF, De Hert S, Kapessidou P, Moerman A, Momeni M, Poelaert P, Rex S, Saldien V, Van Obbergh L, Sermeus L.

Corresponding author : Matthias Desmet.
E-mail : Matthias.Desmet@azgroeninge.be

Paper submitted on June 2, 2020 and accepted on June 16, 2020.
Conflict of interest : None.

clinical practice of peripheral nerve blocks in the adult patient." (2).

Clinical Guidelines

TOPIC 1 : Medicolegal aspects

— Information and informed consent

The patient should be adequately informed in accordance with the recommendations legally defined in the Royal Decree of the 22nd August 2002 (Chapter III, art. 5-11).

Patients should be clearly informed regarding the risks and benefits of the RA procedure that will be performed (3,4). This can be done through a written leaflet, video material or during a preoperative visit. Concerns and questions should be adequately addressed. An example of such an information leaflet is available on the BARA website (www.BARA2001.be).

Information regarding preoperative guidelines (e.g. fasting rules, continuation of medication, …) should be given according to current medical knowledge.

To document the information process, a documented informed consent should be obtained from the patient. This informed consent should not be different from the informed consent for "Anesthesia and/or Sedation", as conversion to general anesthesia is always a possibility.

— Block registration

The working group highly recommends to register the block procedure in the medical record of the patient. All aspects of the block (or blocks if multiple blocks were performed in the same patient) including possible adverse events should be noted. For purposes of quality control, the development of an electronic database is highly recommended. An example of such a registration form is available on the BARA website (www.BARA2001.be).

TOPIC 2 : Preoperative organization

— Fasting Guidelines

Fasting guidelines should be respected when PNBs are performed for elective surgery. This includes surgical procedures performed under PNB (with or without sedation) or when PNBs are performed for postoperative analgesia and thus combined with general or neuraxial anesthesia. Specific fasting guidelines are provided by the European Society of Anesthesiologists (5).

Adherence to fasting guidelines when blocks are performed for analgesic (non-surgical) indications e.g. PNBs for hip fracture analgesia, is not mandatory as it will lead to an unnecessary delay of adequate pain relief.

— Intravenous access and patient monitoring

Obtaining intravenous access is mandatory before any procedure including performance of PNBs.

Monitoring guidelines for standard patient care apply to all patients receiving general anesthesia, RA or procedural sedation. The anesthesiologist must ensure that appropriate monitoring equipment is available and working properly. The following monitoring equipment is required and should be attached before the start of the procedure :

- Pulse oximeter
- Non-invasive (or invasive) blood pressure measurement
- Electrocardiography

Patients should be monitored during the entire peripheral nerve block procedure and according to expert opinion, it is recommended to keep the patient monitored at least 30 minutes or longer after performance of the block according to clinical judgment.

— Block room organization

Some centers benefit from a dedicated "block room" but regional blocks can also be performed in the preoperative holding area, the recovery, or in the actual operating room. Regardless of the location, all necessary requirements regarding monitoring, staffing, resuscitation equipment and drugs should be respected.

Block rooms with dedicated staff aim to increase the quality of RA programs as more blocks can be performed by or under supervision of a skilled anesthesiologist. It aims to reduce failure rates, improve safety profiles, provide teaching opportunities and improve the overall patient experience. In addition to these benefits, a dedicated block room increases theatre turnover and efficiency, leading to significant time and cost savings (6).

The block room must be located in the operating theatre and should offer a quiet environment for patients. It should have all necessary features such as monitoring devices, anesthetic and resuscitation drugs and equipment.

A specific storage cart with all the necessary equipment and drugs, which should be appropriately labeled and readily identifiable, greatly enhances work place organization (6,7).

Block related equipment and drugs :

- Surgical caps, masks and gowns, sterile gloves, sterile drapes, dressings, antiseptic solutions, sponges/gauze, (sterile) marking pen and ruler for landmark identification, sterile ultrasound covers and gel, hypodermic needles for skin infiltration, specific nerve block needles and catheters, syringes, intravenous catheters and intravenous fluids.
- A selection of sedative drugs and opioids for patients requiring sedation.
- A selection of local anesthetics (LA). Ideally, LAs are stored in a separate compartment from other drugs to reduce possible drug error.

Resuscitation Equipment :

- Oxygen supply and different types of oxygen-masks.
- Oral airways of different sizes, laryngeal masks and endotracheal tubes.
- Laryngoscopes with different blades.
- Bag-mask ventilation device.
- Suction.
- Defibrillator.

Resuscitation Drugs :

- Atropine
- Adrenaline
- Ephedrine
- Phenylephrine
- Intralipid® 20%

Ideally, Intralipid should be kept in a container with a protocol for use and equipment to draw up the drug for immediate administration to the patient.

Other resuscitation equipment and drugs (e.g. difficult airway equipment, antiarrhythmic drugs) must be readily available on request.

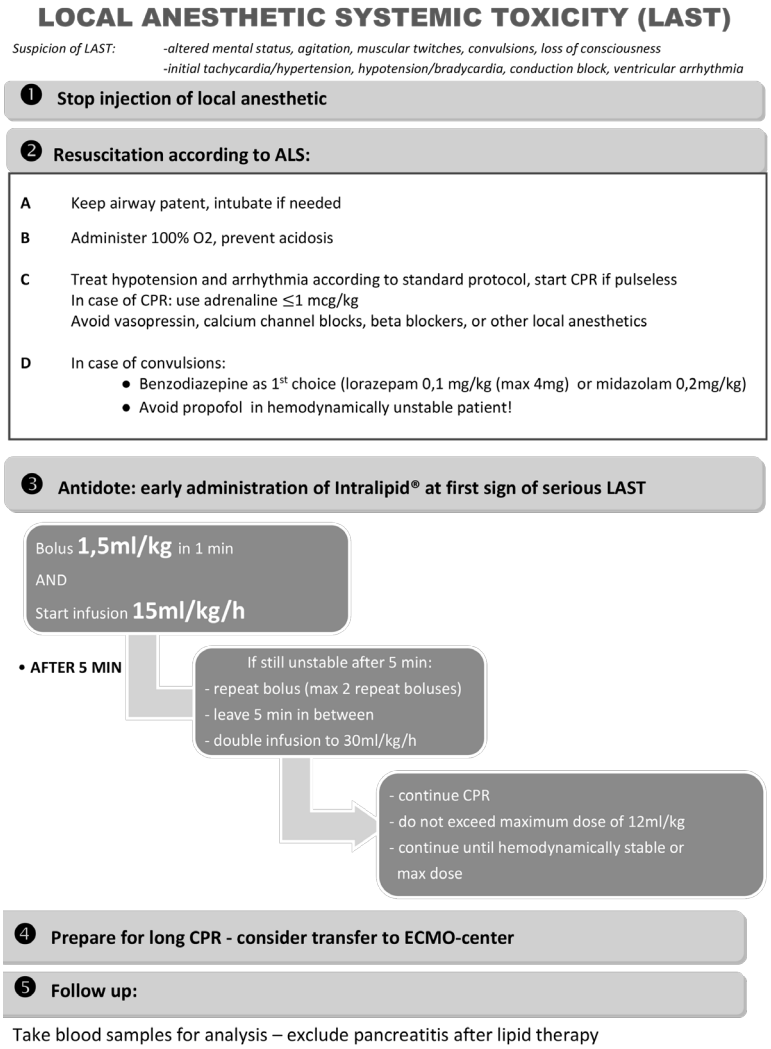

Figure 1. — LAST flowchart

— LA Systemic Toxicity

Although exceedingly rare, local anesthetic systemic toxicity (LAST) remains a feared complication related to PNBs (8). The most important recommendation is that all involved in the care of patients receiving PNBs should be vigilant and prepared to detect and treat LAST. We would like to emphasize that during general anesthesia, patients may present only with cardiac symptoms, as neurological symptoms remain often undetected due to the effects of anesthetics or sedatives (9). We recommend to regularly educate all those involved in placement and follow up of patients with PNBs (anesthesiologists, OR/PACU nurses and floor nurses) regarding the presentation and treatment of LAST. We recommend that a protocol regarding the treatment of LAST is available and clearly visible in the different locations where PNBs are performed or where patients that received a PNB are treated. As mentioned above, a 20% lipid emulsion should be readily available at all times (10). An example of the LAST protocol is available on the BARA website (www.BARA2001.be) and in Figure 1. We strongly recommend the registration of potential LAST events on the website www.lipidrescue.org.

— Sedation

It is probably preferable to perform PNBs in awake patients. There is nonetheless no evidence that PNBs performed in patients under general anesthesia, neuraxial block or deep sedation carry greater risks than when performed in awake or lightly sedated patients if all safety precautions are taken to minimize the risk of complications (11). However, the inherent risks of deep sedation and anesthesia will be added to the risks associated with PNBs. Therefore, the anesthesiologist should carefully outweigh the risks and benefits of performing a PNB in an awake or lightly sedated patient versus performing the block in a deeply sedated or anesthetized patient. The decision to perform a PNB has to be made on a case by case basis. The following points require consideration in this decision process : indication of the PNB, performance by an experienced anesthesiologist, availability of appropriate equipment and the consent of the patient after a clear explanation of the risks and benefits.

— Time out : STOP before you BLOCK procedure

In order to reduce the incidence of wrong-sided blocks, we advise to follow the WHO checklist prior to every PNB. Patient details, type and side of block as well as surgical site marking should be confirmed. Immediately before inserting the needle, a time out procedure must be performed where block details are confirmed by the anesthesiologist, the assisting nurse and, if possible, the patient. This procedure is described in the STOP before you BLOCK publication (12).

TOPIC 3 : Block technique

— Asepsis

When performing a PNB, adherence to standard asepsis guidelines is recommended (13, 14, 15).

With the exception of the role of antiseptic solutions, studies examining the role of asepsis during peripheral nerve block are lacking. Most recommendations to control infectious complications associated with PNBs are based on existing literature and guidelines for the prevention of epidural or intravascular catheter-related infection or derived from guidelines for prevention of surgical site infections.

Sterile surgical gloves should be used, not only to protect patients from cross-contamination, but also the health care worker from blood-borne pathogen exposure.

Wearing a surgical cap and mask, has been found to significantly reduce contaminations from micro-organisms growing in the upper airway of clinicians during neuraxial blockade. While the risks and consequences of infectious complications after neuraxial blockade cannot be compared with single shot PNBs, the panel recommends using cap and mask during both single shot and catheter procedures. These recommendations also apply for those assisting the anesthesiologist with the procedure.

In analogy with central line insertion, maximal barrier precautions should be taken while performing a catheter technique. This includes, in addition to the previously mentioned precautions, the use of sterile gowns and drapes.

For all peripheral nerve block techniques adequate skin antisepsis should be performed. Alcohol-based 0,5% chlorhexidine is considered as the antiseptic of choice to prepare the skin before regional anesthetic techniques. The application must be broad around the injection site and an adequate drying time should be respected to avoid subdermal introduction of the antiseptic with a risk of neurotoxicity (16).

Bacterial filters may be considered during extended continuous peripheral nerve block infusion. Periodically checking the catheter insertion place for signs of infection is mandatory. Infection risk with catheter use increases over time, especially after four days (17).

We strongly recommend against the performance of PNBs (single shot or catheters) in patients where there is a local infection of the insertion place (13).

When using ultrasound, special attention is required to ensure an adequate aseptic technique as both the ultrasound coupling gel and transducers can be sources of nosocomial infection.

The ultrasound equipment must be cleaned and disinfected between procedures according to specific institutional policy and manufacturers guidelines. A sterile ultrasound cover is the simplest solution to avoid infection and transmission from one patient to another (18). Alternatively, for single-shot PNBs, a sterile adhesive transparent dressing can be used assuming this can be applied aseptically (19). If a catheter is placed, a sterile cover with sleeve should be used, covering all portions of the ultrasound cord that might come in contact with the procedural field.

We recommend the use of sterile ultrasound gel when performing a PNB as tearing of the protective cover around the ultrasound probe when using non-sterile ultrasound gel would break asepsis. Use of RA packs, which contain prepared sterile equipment may help to become familiar to the aseptic technique.

— Performance of PNB and prevention of peripheral nerve injury (PNI)

Although the occurrence of severe PNI is rare, the performance of a PNB has an intrinsic risk of PNI (20). It is important to acknowledge that the vast majority of perioperative neurological complications are the result of non-PNB related causes (21, 22). However, safety precautions are recommended to reduce the risk of PNI to a minimum. Although intraneural extrafascicular needle positioning or injection does not consistently lead to functional nerve injury, histological changes may occur. More importantly, these changes can be caused by mere needle-nerve contact. Where histological changes often remain subclinical in healthy patients. These changes may be aggravated in patients with pre-existing neurological conditions, leading to clinical symptoms. Therefore, as a precaution measure, needle nerve contact and/or intraneural needle placement should be avoided (20).

— Equipment for nerve localization and prevention of peripheral nerve injury

Current evidence does not support superiority of one technique or device over another in terms of performing PNB and prevention of PNI. A combination of different techniques, devices and safety measures is advised (20).

Paresthesia : nerve contact/puncture may frequently occur without paresthesia. Using paresthesia as the sole guidance tool for nerve localization is therefore unreliable and is unacceptable according to current standards (23).

Nerve stimulation (NS) : presence of an evoked motor response (EMR) at currents between 0.3 and 0.5mA may indicate intimate needle-nerve contact or intraneural needle tip position. Avoid injection when an EMR is present at a current of 0.5mA or less. Absence of an EMR does not exclude needle-nerve contact or intraneural needle tip placement (24).

Ultrasound guidance : evidence supports the use of ultrasound compared to the use of NS alone. It increases block success including a faster onset of a PNB, decreases intravascular injections and the concomitant risk of LAST and facilitates teaching of PNBs (25, 26, 27). Ultrasound can but does not always detect intraneural needle tip placement and/or injection (28). Current evidence does not demonstrate a reduction of PNI by the use of ultrasound alone (29).

Opening injection pressure (OIP) monitoring : animal and cadaver data have linked high injection pressures (>20psi) to intrafascicular injections (30, 31). Research has demonstrated that a low OIP (<15psi) is associated with safe injections in non-neural tissue (32). However, due to the low incidence of post peripheral nerve block injury, robust in vivo human data confirming the effectiveness of pressure monitoring to prevent PNI is lacking (33). Furthermore, the debate regarding the ideal pressure monitoring system is ongoing. Subjective 'syringe-feel' pressure monitoring has been proven inaccurate (34). Unfortunately, in line pressure monitor devices do not reliably represent the pressure at the tip of the needle (35). Although, robust evidence is lacking, the working group considers pressure monitor devices valuable tools to increase safety for which further research is needed (33).

Needle type : we recommend the use of short-bevel needles as nerve and fascicle puncture are less likely to occur (36).

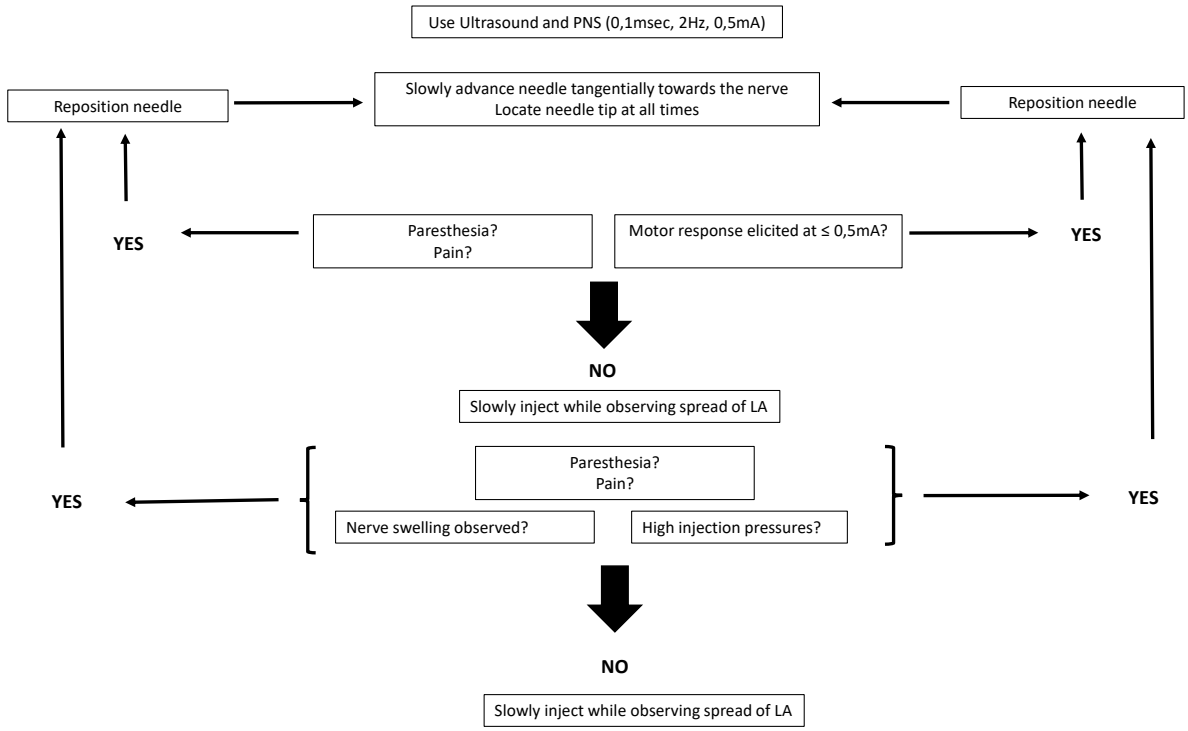

Figure 2. — Flowchart for performance of PNB.

— Needling Technique

Both in-plane and out-of-plane needling techniques can be used during ultrasound guided PNBs. However, the trajectory of the needle tip can be followed during the entire procedure with an in-plane technique.

According to the PNB working group the following points require special attention during the performance of PNB (Figure 2) :

- Always advance the needle slowly.
- The performer should be aware of the location of the needle tip at all times.
- A tangential approach to the nerve may minimize the possibility of nerve puncture (37).
- Use hydrolocalization and/or hydrodissection to confirm correct needle positioning and spread of LA, this advice is even more pertinent when performing fascial plane blocks.
- The presence of paresthesia or pain should prompt cessation of needle advancement or injection and the needle should be repositioned before injection.
- Reposition the needle when an EMR is obtained with a current of 0.5mA or less.
- Stop the injection and reposition the needle when nerve swelling is observed during injection.
- Avoid injections against high pressure (30).
- Follow the spread of the LA throughout the injection.

— Prevention of LA systemic toxicity

It has been demonstrated that ultrasound reduces the incidence of LAST (27). The use of Color Doppler mode to visualize vessels in the needle trajectory before puncturing is recommended to minimize inadvertent intravascular injection and subsequent systemic toxicity.

Aspiration before injection and after every needle repositioning should be performed and fractionated injections of small volumes (<5mL) with repeated aspiration are recommended. Forceful aspiration should be avoided as it could lead to false negative aspiration. Be aware of vein and even artery compression by forceful application of the ultrasound probe, which may impede aspiration of blood while injection is still possible in a compressed vein. It is important to trace spread of the LA solution with ultrasound during the entire procedure. Failure to detect the LA solution during injection can be a marker of intravascular injection.

Epinephrine can be used as a marker of intravascular injection when used as an adjuvant in a concentration of 1/200.000. A minimal of 15 micrograms intravenously is necessary to detect an increase in heart rate of 15/min and pulse pressure of 10 mmHg (10).

Table 1
Maximum recommended doses of LA.

Local Anesthetic	Plain		With epinephrine	
Bupivacaine	2 mg.kg^{-1}	175 mg	3 mg.kg^{-1}	225 mg
Levobupicaine	2 mg.kg^{-1}	200 mg	3 mg.kg^{-1}	225 mg
Lidocaine	5 mg.kg^{-1}	350 mg	7 mg.kg^{-1}	500 mg
Mepivacaine	5 mg.kg^{-1}	350 mg	7 mg.kg^{-1}	500 mg
Ropivacaine	3 mg.kg^{-1}	200 mg	3 mg.kg^{-1}	250 mg
Prilocaine	6 mg.kg^{-1}	400 mg	8 mg.kg^{-1}	600 mg

Concentrations of 5 micrograms per milliliter (1/200.000) are not associated with ischemic (neurotoxic) effects in healthy patients, data regarding safety of epinephrine in patients with pre-existing neuropathies are lacking (38).

— Advice on the use of additives and against the mixing of LAs

Perineural additives are widely used in regional anesthesia and analgesia. They are used to prolong the duration of the block, reduce pain scores, reduce analgesic requirements and improve overall patient satisfaction. However, these benefits must be balanced against the neurotoxic potential of additives and their undesirable systemic effects.

It is important to note that all commonly used additives for PNBs are not licensed for perineural use. The working group only provides information regarding the most effective additives.

Dexamethasone, a long-acting glucocorticoid, prolongs the analgesic duration of a PNB regardless of the route of administration. In the absence of evidence confirming the safety of perineural dexamethasone, intravenous administration is recommended as it similarly prolongs analgesia compared to perineural administration. An intravenous dose of 0.1mg/kg of dexamethasone is recommended to prolong analgesia with 8 hours (39).

The alpha receptor agonists clonidine (2hrs) and dexmedetomidine (6hrs) effectively prolong the duration of analgesia after perineural administration. Clonidine and to a lesser extent dexmedetomidine, is however associated with a high incidence of undesirable systemic effects such as bradycardia, hypotension and sedation (40, 41).

The partial μ-opioid receptor agonist buprenorphine prolongs the duration of analgesia with 6 hours, however its perineural use is associated with a 5 times higher incidence of PONV compared to a control group (42).

In accordance to recent international recommendations, the mixing of LAs is not advised (13). The presumed benefits like shortened onset times and block success could not be demonstrated in the literature. Furthermore, clinicians should be aware of the potential of additive toxic effects (43).

— Maximum doses of LAs

Maximum recommended doses have been advised by manufacturers, but their scientific basis has been questioned. Plasma concentrations differ according to the rate of absorption which depends on the site of injection (Rate of absorption : intrapleural > intercostal > caudal > epidural > brachial plexus > femoral/sciatic > subcutaneous > intra-articular > spinal) and the injection technique (44). Other risk factors for toxicity are extremes of ages, total mass of LA deposition, low protein binding, cardiac conduction disorders, heart failure with low perfusion states, hepatic dysfunction, metabolic diseases such as uremia with metabolic acidosis (10). As definitive recommendations regarding doses cannot be provided, the working group urges clinicians to use the lowest effective dose when performing a PNB. Subgroups of patients (e.g. pregnant, frail, malnourished, pediatric patients, the elderly and patients with hepatic or renal disease) have an increased risk of systemic toxicity as higher free plasma fractions of LAs can occur, these subgroups require special attention and vigilance.

The maximum recommended doses presented in Table 1 may serve as a general guideline.

— Neurotoxicity of LAs

The neurotoxic potential of LAs has been extensively described in both in vitro and in vivo studies (45, 46). The use of higher concentrations and longer exposure times play an important role in the pathophysiological processes (44). The working

group recommends the use of the lowest effective concentration of LAs, especially when continuous techniques are used (Table 1) (20, 47).

Patients with pre-existing neuropathies are particularly at risk of nerve injury induced by LAs. In these patients PNBs can be used, however a risk benefit analysis should be performed by the clinician and the patient should be informed of the higher risks.

— Exclusion criteria of peripheral nerve blocks

The sole absolute contraindications for PNB performance are refusal of the patient and infection at the puncture site. Regarding the performance of PNBs in patients receiving antithrombotic or thrombolytic therapy, we would like to refer to the guidelines provided by the American Society of Regional Anesthesia and Pain Medicine which have been recently updated (48).

Relative contraindications can be patient related (e.g. pre-existing neuropathies, diabetes, alcoholism, previous chemotherapy, …) or block related (e.g. interscalene block for patients with severe pulmonary pathology, femoral nerve block and need for early mobilization). In these patients PNBs can be used however a risk benefit analysis should be performed by the clinician and the patient should be informed of the higher risks.

TOPIC 4 : Postoperative Care

Peripheral nerve blocks provide superior pain relief with a lower incidence of side effects leading to faster and higher quality recovery and rehabilitation compared to general anesthesia. Patients recovering from PNBs must meet the same discharge criteria as patients recovering from general anesthesia. However, these patients must also fulfill additional criteria to ensure safe ambulation especially after lower limb nerve blocks. Furthermore, patients and their direct caregivers will need specific instructions on discharge from the hospital.

— PACU discharge criteria

The post-anesthesia care unit (PACU) is an expensive and labour-intensive environment. PNBs may allow a complete bypass of the PACU in the ambulatory setting. The use of an objective assessment tool with predefined discharge criteria is recommended. As many patients will fulfill the criteria for immediate discharge after surgery, the PACU can be bypassed in selected cases. We strongly recommend that patients are monitored at least 30 minutes after block performance. Further follow up after PACU discharge is strongly recommended, especially in patients with peripheral nerve catheters. This follow-up should be performed according to local policy, preferably by an Acute Pain Service providing 24/7 care.

— Hospital discharge criteria and recommendations

Similar to PACU discharge, post anesthesia scoring systems can be used for discharge from the hospital, the modified PADSS (post anesthesia discharge scoring system) is an example of such a discharge score. However, certain points require special attention and the working group recommends that patients are adequately informed regarding the risks and expected postoperative course after PNBs.

After single-injection nerve blocks, patients should be warned of the consequences of the effects of a sensory and motor block. Patients should be advised to respect the necessary precautions to prevent self-inflicted harm. Patients who undergo upper extremity blocks should be discharged with a protective sling. Patients with femoral nerve or lumbar plexus blocks and persistent quadriceps weakness at the time of discharge should be sent home with a knee immobilizer, crutches and the advice not to bear weight on the affected extremity.

Furthermore, information on the natural course of resolution of the peripheral nerve block should be provides as well as signs of possible nerve injury. These include new onset of pain, weakness, numbness, paresthesia or other abnormal sensations lasting beyond the expected duration of the specific block. Finally, an adequate analgesic regimen should be prescribed and patients should be informed on the postoperative analgesic protocol, including intake of analgesics prior to the expected resolution of the block.

For patients with continuous PNBs, the decision to send a patient home with a portable perineural infusion should be made very carefully following a strict protocol. Successful management of CPNB catheters at home should include detailed written instructions, daily telephone follow-up and contact information of a healthcare provider familiar with these techniques who is available 24/7.

— Follow up after discharge

It is advised to follow up on the patient the next day to assess block resolution or persistent symptoms, current level of pain, adequacy of pain

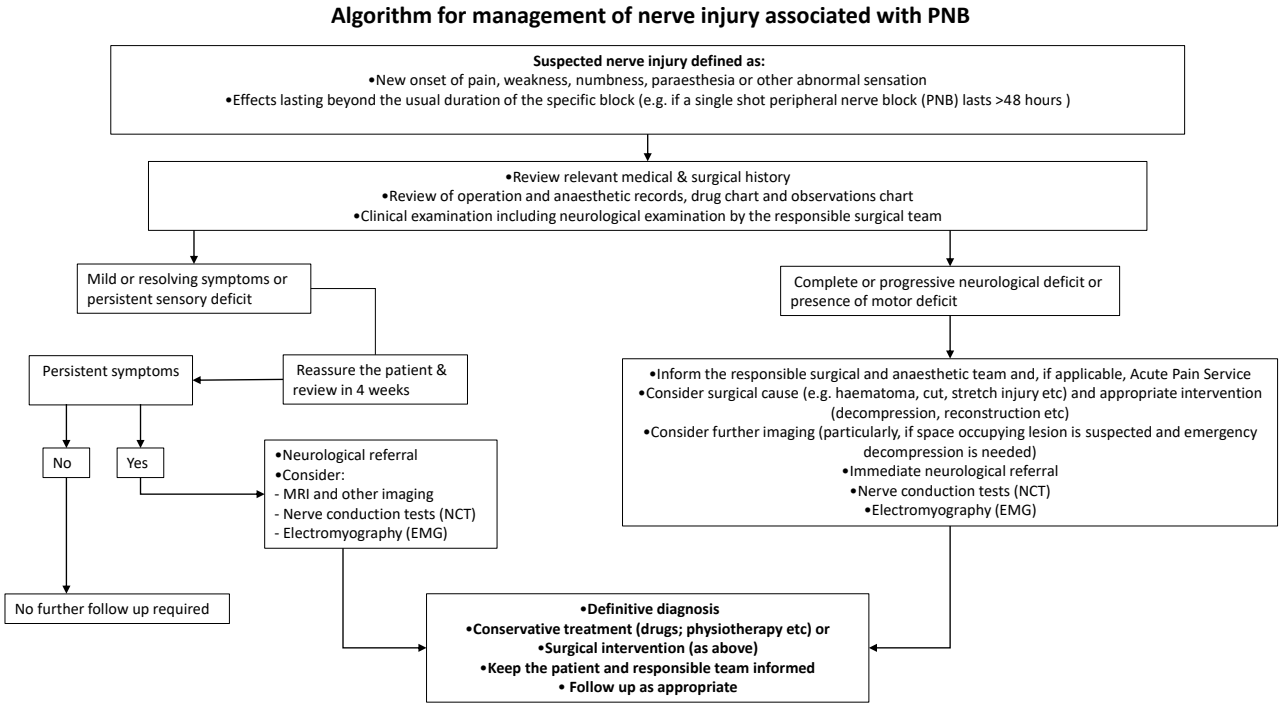

Figure 3. — Algorithm for management of nerve injury associated with PNB. Adapted with permission from RA-UK.

relief, and overall satisfaction with postoperative recovery.

TOPIC 5 : Peripheral nerve injury

— Incidence and risk factors

Early transient postoperative neurological symptoms such as paresthesia occur frequently with an incidence up to 15%. Fortunately, neurological symptoms resolve over time (0-2.2%, 0-0.8%, 0-0.2% at three, six and twelve months respectively) and rarely result in permanent injury (0.014-0.04%) (20, 22, 49)

As it is beyond the scope of these guidelines, the working group refers to the extensive description of the pathophysiological mechanisms by Brull et al. (29).

Peripheral nerve blocks are not an independent risk factor for peri-operative nerve injury. Peri-operative nerve injury can be linked to positioning, surgical, anesthetic or patient related factors. The risk is higher after orthopedic, cardiac, and neurosurgical procedures and in patients with specific comorbidities (e.g. pre-existing neuropathies, diabetes, extremes in weight, tobacco use, hypertension, …). Pre-existing neuropathies should be evaluated on an individual basis. They are present in 2-8% of the general population, increasing to 58% of patients with type I diabetes (49).

— Symptoms and follow up management

Symptoms of suspected PNI may be highly variable in onset and severity and may range from mild paresthesia and numbness to severe persistent pain or full sensory and motor loss. In such patients the medical and anesthetic file should be thoroughly reviewed. A complete clinical neurological examination with special attention to the distribution of symptoms is important to evaluate the location and etiology of a possible injury. This will often allow clinicians to differentiate block related nerve injury from other causes of peripheral nerve injury (e.g. peroperative compression neuropathies).

Prompt risk stratification to identify cases that require urgent attention is essential. Possible reversible factors (e.g. extrinsic compression by tight dressing, compartment syndrome, hematoma) should be immediately identified and appropriately managed. Urgent imaging (ultrasound, CT-scan) or compartment pressure measurement can be considered in selected cases. Recognition of nerve injury may be delayed in cases with excessive sedation, pain, strong analgesics, continuous catheters or in ambulatory surgery.

The working group strongly advises to develop a protocol on the management of suspected PNI injury. This protocol should include the following recommendations :

- Focus on patient information and support, remain available for short and long term follow up during the course of PNI.
- If only mild sensory symptoms are present in the distribution area of the block or a known site of compression, the patient can be reassured and reviewed in 4 weeks by a neurologist.
- If complete or progressive sensory or motor deficit is present, or if the deficit is difficult to localize then early neurologic consult and follow up is advised. Electrophysiological studies (nerve conduction tests, electromyography), performed by the neurologist, can only reveal abnormalities after 3 weeks, when sufficient signs of Wallerian degeneration appear. Nevertheless, those studies can be requested earlier to provide a baseline electromyography (EMG) and as EMG changes can detect and differentiate with preexisting neuropathies.
- There is no evidence of any pharmacological therapy to enhance neuro-regeneration. Only conservative measures like analgesics and physical therapy to maintain muscle mass and prevent contractures are beneficial.
- When no improvement occurs after 3-5 months, referral to a peripheral nerve surgeon should be considered.

[Figure 3 : Management algorithm of suspected PNI]

References

1. Sermeus L, Pirson A, Breebaart B, Decoster J, Dereeper E, Gautier Ph and Guntz E, et al. et. 2013. Clinical guidelines for the practice of peripheral nerve blocks in the adult. Acta Anaesth. Belg. 64:105-108.
2. Bonhomme V, Wouters P, Foubert L, Van de Velde M, Brichant JF, De Hert S and Kapessidou P, et al. 2020. Belgian standards for patient safety in anesthesia. Revision 2019 of the last version published in the Acta Anaesthesiologica 2002, 53(1) :5-9. Acta Anaesth. Belg. 71:5-14.
3. Yentis SM, Hartle AJ, Barker IR, Barker P, Bogod DG and Clutton-Brock TH, et al. 2017. AAGBI : Consent for anaesthesia 2017. Anaesthesia 72:93-105.
4. Tierney S and Perlas A. 2018. Informed consent for regional anesthesia. Curr Opin Anesthiol 31:614-621.
5. Smith I, Kranke P, Murat I, Smith A, O'Sullivan G, Søreide E and Spies Claudia, et al. 2011. Perioperative fasting in adults and children : guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol 28:556-569.
6. Chazapis M, Kaur N and Kamming D. 2014. Improving the Peri-operative care of Patients by instituting a 'Block Room' for Regional Anaesthesia. BMJ Open Quality 3:u204061. w1769. doi : 10.1136/bmjquality.u204061.w1769
7. Mariano ER. 2008. Making It Work : Setting up a Regional Anesthesia Program that Provides Value. Anesthesiol Clin. 6:681-692.
8. Weinberg G and Barron G. 2016. Local Anesthetic Systemic Toxicity (LAST) : Not Gone, Hopefully Not Forgotten. Reg Anesth Pain Med. 41:1-2.
9. Gitman M and Barrington MJ. 2018. Local Anesthetic Systemic Toxicity. A Review of Recent Case Reports and Registries. Reg Anesth Pain Med. 34:1111-1119.
10. Neal JM, Barrington MJ, Fettiplace MR, Gitman M, Memtsoudis SG, Mörwald EE and Rubin DS, et al. 2018. The Third American Society of Regional Anesthesia and Pain Medicine Practice Advisory on Local Anesthetic Systemic Toxicity. Executive Summary 2017. Reg Anesth Pain Med. 43:113-123.
11. Kessler P, Steinfeldt T, Gogarten W, Schwemmer U, Büttner J, Graf BM and Volk T. 2013. Peripheral regional anesthesia in patients under general anesthesi : risk assessment with respect to paresthesia, injection pain and nerve damage. Anaesthesist. 62:483-8.
12. Moppett I and Shorrock S. 2018. Working out wrong-side blocks. Anaesthesia. 73:407-411.
13. Carles AM, Beloeil H, Bloc S, Nouette-Gaulain K, Aveline C and Cabaton J, et al. 2016. Anesthésie Loco-Régionale périnerveuse (ALR-PN) Expert panel guidelines on perineural anesthesia. Conseil d'Administration de la SFAR
14. Hebl JR and Niesen AD. 2011. Infectious complications of regional anesthesia. Curr Opin Anesthesiol 24:73-580.
15. Hebl JR. 2006. The Importance and Implications of Aseptic Techniques During Regional Anesthesia. Reg Anesth Pain Med. 31:311-323.
16. Campbell JP, Plaat F, Checketts MR, Bogod D, Tighe S and Moriarty A, et al. 2014. Safety guideline : skin antisepsis for central neuraxial blockade. Anaesthesia. 69:1279-1286.
17. Bomberg H, Bayer I, Wagenpfeil S, Kessler P, Wulf P and Standl T, et al. 2018. Prolonged Catheter Use and Infection in Regional Anesthesia. Anesthesiology 4:764-773.
18. Marhofer P, Schebesta K and Marhofe D. 2016. Hygieneaspekte in der ultraschallgestützten Regional anästhesie. Anaesthesist. 65:492-498.
19. Alakkad H, Naeeni A, Chan VWS, Abbas S and Oh J, et al. 2015. Infection Related to Ultrasound-Guided Single-Injection Peripheral Nerve Blockade A Decade of Experience at Toronto Western Hospital. Reg Anesth Pain Med. 40:2014-2016.
20. Neal JM, Barrington MJ, Brull R, Hadzic A, Hebl JR and Horlocker TT, et al. 2015. The Second ASRA Practice Advisory on Neurologic Complications Associated With Regional Anesthesia and Pain Medicine. Reg Anesth Pain Med. 40:401-430.
21. Barrington MJ, Watts SA, Gledhill SR, Thomas Rd, Said SA and Snyder Gl, et al. 2009. Preliminary Results of the Australasian Regional Anaesthesia Collaboration. Reg Anesth Pain Med. 34:534-541.
22. Welch MB, Brummett CM, Welch TD, Welch TD, Tremper KK, Shanks AM, Guglani P and Mashour GA. 2009. Perioperative Peripheral Nerve Injuries A Retrospective Study of 380,680 Cases during a 10-year Period at a Single Institution. Anesthesiology. 111:490-497.
23. Neal JM. 2001. How close is close enough? Defining the "paresthesia chad". Reg Anesth Pain Med. 26:97-99.
24. Vassiliou T, Müller HH, Limberg S, De Andres J, Steinfeldt T and Wiesmann T. 2016. Risk evaluation for needle-nerve contact related to electrical nerve stimulation in a porcine model. Acta Anaesthesiol Scand. 60:400-406.
25. Koscielniak-Nielsen ZJ. 2008. Ultrasound-guided peripheral nerve blocks : what are the benefits? Acta Anaesthesiol Scand. 52:727-737.
26. Abrahams MS, Aziz MF, Fu RF and Horn JL. 2009. Ultrasound guidance compared with electrical neurostimulation for peripheral nerve block : a systematic review and meta-analysis of randomized controlled trials. Br J Anaesth. 102:408-417.
27. Barrington MJ and Kluger R. 2013. Ultrasound guidance reduces the risk of local anesthetic systemic toxicity

following peripheral nerve blockade. Reg Anesth Pain Med. 38:289-297.
28. Krediet AC, Moayeri N, Bleys RLAW and Groen GJ. 2014. Intraneural or Extraneural. Reg Anesth Pain Med. 39:409-413.
29. Brull R, Hadzic A, Reina MA and Barrington MJ. 2015. Pathophysiology and Etiology of Nerve Injury Following Peripheral Nerve Blockade. Reg Anesth Pain Med. 40 :479-490.
30. Hadzic A, Dilberovic F, Shah S, Kulenovic A, Kapur E and Zaciragic A, et al. Combination of intraneural injection and high injection pressure leads to fascicular injury and neurologic deficits in dogs. Reg Anesth Pain Med. 29:417-423.
31. Vermeylen K, Hermans M, Soetens F, Vereecke E, Steinfeldt T and Groen G, et al. 2017. Opening Injection Pressure Is Higher in Intraneural Compared With Perineural Injections During Simulated Nerve Blocks of the Lower Limb in Fresh Human Cadavers. Reg Anesth Pain Med. 42:362-367.
32. Gadsden J, Latmore M, Levine DM and Robinson A. 2016. High Opening Injection Pressure Is Associated With Femoral Nerve Block. Reg Anesth Pain Med. 41:1-6.
33. Barrington MJ and Lirk P. 2019. Reducing the risk of neurological complications after peripheral nerve block : what is the role of pressure monitoring? Anaesthesia. 74:9-12.
34. Theron PS, Mackay Z, Gonzalez JG, Donaldson N, Blanco R. 2009. An Animal Model of "Syringe Feel" During Peripheral Nerve Block. Reg Anesth Pain Med. 34:330-332.
35. Saporito A, Quadri C, Kloth N and Capdevila X. 2019. The effect of rate of injection on injection pressure pro fi les measured using in-line and needle-tip sensors : an in-vitro study. Anaesthesia. 74:64-68.
36. Sala-Blanch X, Ribalta T, Rivas E, Carrera A, Gaspa A and Reina MA, et al. 2009. Structural injury to the human sciatic nerve after intraneural needle insertion. Reg Anesth Pain Med. 34:201-205.
37. Sermeus LA, Sala-Blanch X, McDonnell JG, Lobo CA, Nicholls BJ and van Geffen GJ, et al. 2017. Ultrasound-guided approach to nerves (direct vs. tangential) and the incidence of intraneural injection : a cadaveric study. Anaesthesia. 72:461-469.
38. Neal JM. 2003. Effects of Epinephrine in Local Anesthetics on the Central and Peripheral Nervous Systems : Neurotoxicity and Neural Blood Flow. Reg Anesth Pain Med. 28:124-134.
39. Albrecht E, Kern C and Kirkham KR. 2015. A systematic review and meta-analysis of perineural dexamethasone for peripheral nerve blocks. Anaesthesia. 70:71-83.
40. Pöpping D, Elia N, Marret E, Wenk M and Tramèr MR. 2009. Clonidine as an Adjuvant to Local Anesthetics for Peripheral Nerve and Plexus Blocks. Anesthesiology. 111:406-415.
41. Abdallah FW and Brull R. 2013. Facilitatory effects of perineural dexmedetomidine on neuraxial and peripheral nerve block : a systematic review and meta-analysis. Br J Anaesth. 110:915-925.
42. Schnabel A, Reichl SU, Zahn PK, Pogatzki-Zahn EM and Meyer-Frießem CH. 2017. Efficacy and safety of buprenorphine in peripheral nerve blocks. Eur J Anaesthesiol. 34:576-586.
43. Spiegel DA, Dexter F, Todd MM, Warner DS and Baker MT. 1992. Central Nervous System Toxicity of Local Anesthetic Mixtures in the Rat. Anesth Analg. 75:922-928.
44. Rosenberg P, Veering B and Urmey W. 2004. Maximum Recommended Doses of Local Anesthetics : a Multi-factorial Concept. Reg Anesth Pain Med. 29:564-575.
45. Yang S, Abrahams MS, Hurn PD, Grafe MR and Kirsch JR. 2011. Local anesthetic schwann cell toxicity is time and concentration dependent. Reg Anesth Pain Med. 36:444-451.
46. Verlinde M, Hollmann MW, Stevens MF, Hermanns H, Werdehausen R and Lirk P. 2016. Local anesthetic-induced Neurotoxicity. Int J Mol Sci. 17:1-14.
47. El-Boghdadly K, Pawa A and Chin KJ. 2018. Local anesthetic systemic toxicity : Current perspectives. Local Reg Anesth. 11:35-44.
48. Horlocker TT, Vandermeulen E, Kopp SL, Gogarten W, Leffert LR and Benzon HT. 2018. Regional Anesthesia in the Patient Receiving Antithrombotic or Thrombolytic Therapy. Reg Anesth Pain Med. 43:263-309.
49. Hewson DW, Bedforth NM and Hardman JG. 2018. Peripheral nerve injury arising in anaesthesia practice. Anaesthesia. 73:51-60.