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Official Title:

"Feasibility and safety of an over-pressure wash-in method using fresh gas flow 0.5 L and Sevoflurane 8% during initiation of low-flow anaesthesia: a prospective, randomised, descriptional study".

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Title

Feasibility and safety of an over-pressure wash-in method using fresh gas flow 0.5 L and Sevoflurane 8% during initiation of low-flow anaesthesia: a prospective, randomised, descriptional study

Introduction and review of literature

Low-flow anaesthesia (LFA) with fresh gas flow (FGF) ≤ 1 L/min has advantages due to relatively lower cost, less environmental burden, and increased humidity and temperature of inspired gas leading to improved mucociliary function of the patient.[1] Any technique that employs a fresh gas flow that is less than the alveolar ventilation can be classified as LFA. The development of modern anaesthetic machines, gas analyser monitors, precision vaporisers and introduction of more potent volatile agents with minimal uptake were some of the breakthroughs encouraging LFA enthusiasts.[2] The staggering amount of environmental pollution due to anaesthetic gases during the present-day practice virtually mandates every anaesthesia provider to take that extra bit of effort to use the available facilities to implement LFA.[3] The idea of LFA is to replenish the consumed gases with as minimum fresh gas as possible while making sure to remove CO_2 before recirculating. This minimises the loss of anaesthetic agents into the environment.[4] The merits of reducing flow must not overrule safety, by maintaining adequate oxygen content in the circle and avoiding hypoxic gas mixture, inadequate anaesthesia control and too light anaesthesia with risk for awareness.[2, 5]

Volatile anaesthetic agents are unique in that it is possible to significantly reduce the mass of drug delivered to the circuit (by lowering FGFs) without altering the amount that actually enters the patient.[6] Studies have shown that 1 L/min change in FGF with Sevoflurane results in a change of between 4 and 18 ml/hour consumption of sevoflurane.[7] The challenge is to control the dynamic equilibrium of FG composition as the uptake and metabolism are time-sensitive and many factors influence the consumption and production of gaseous components. This can be achieved only through frequent adjustments in the gas flow controls.[1]

LFA requires flow meters calibrated to low flow down to 50 ml/min, leak-proof circle breathing system and airway devices like cuffed endotracheal tube (ETT), gas monitoring system providing inspired and end-tidal concentrations of agent, vapourisers capable of delivering high concentrations and calibrated to be accurate at low FGF. Since low FGFs are added to significantly large reserve volume (approximately 9-10 litres), consisting of breathing tubing, reservoir bag, anaesthetic ventilator, intergranular space, etc., in addition to functional residual capacity (FRC) of the patient, it requires 3-time constants (calculated by reserve volume divided by FGF) to effect 95% change in gas composition to occur. However, once steady state is achieved, LFA provides the most economic use of anaesthetic agents. Sevoflurane when used with strong base-free CO_2 absorbent is suitable for use in LFA because it has low blood-gas solubility. The minimum alveolar concentration (MAC) of Sevoflurane varies with

patient age, from 1.4% at age 80 years to 2.3% at age 1 year.[8] The optimal alveolar concentration of Sevoflurane (F_AS) to prevent motor movement and autonomic response during anaesthesia is MAC-Bar which approximates 1.5 MAC. Thus, the target of F_AS during anaesthesia in daily practice varies between 1 to 3.5%, depending on the adjuvant drugs used.

Since use of low FGF leads to a long time constant, a wash-in phase using a high FGF and high vapouriser concentration (F_V) of volatile anaesthetic is warranted in order to rapidly achieve the required concentration of inhalation anaesthetic in the breathing system.[8] Conventionally LFA is administered using high flows initially up to 4-10 L/min for 3-time constants (approximately 3 minutes) with Sevoflurane dial setting of 0.8-2.5% to bring the circuit to the desired concentration, then the flows are reduced for maintenance of anaesthesia. In this method of initial high flows, there is risk of delivering high anaesthetic concentrations during induction of anaesthesia and wastage of volatile agents when the total consumption of anaesthetic agent (AA) is calculated at the end of surgery.

Wash-in is the time taken to reach 1 MAC concentration. Sevoflurane wash-in schemes lack simplicity, target coverage and applicability. Various studies have demonstrated that the time to reach 1 MAC decreased at higher flow rates (1-2-4) but plateaued at 4-4.8 L/min. Lindqvist et. al.[9] reported a 2-step wash-in technique to achieve a F_AS of 1.2%; starting with FGF 1 $L \cdot min^{-1}$ and F_VS 8% for 1 min, then reducing FGF to 1, 0.7, 0.5, and 0.3 $L \cdot min^{-1}$. They found that the respective time to achieve the target F_AS was 1.8, 1.5, 2.5 and 3.6 min. Horwitz et. al.[10] reported that by using a FGF of 1.0 or 0.5 $L \cdot min^{-1}$ with a F_VS 6% during the wash-in, the respective time to reach 1 MAC was 6.2 ± 1.3 and 15.2 ± 2.4 min and up to 1.5 MAC at 7.5 ± 2.5 and 19 ± 4.4 min. Shin et al.[11] performed a wash-in study using a Primus anaesthetic machine connected to a test-lung, using a FGF of 0.5, 1, and 3 $L \cdot min^{-1}$ and setting the F_VS to 6%. The respective mean time to reach a F_AS of 4% for each FGF was 1165, 534, and 155 s. Nel MR et. al.[12] have shown while using FGF=6 L (Nitrous Oxide 4L + O_2 2L) and Sevoflurane vapouriser dial set at 2.5% that equilibration point defined as F_E/F_I=0.8 (corresponding to F_AS=2%) can be reached in a mean (standard deviation) of 8.2 ± 2.1 min. Tribuddharat S et. al.[8] studied the 1-1-8 wash-in scheme with FGF=2L (O_2 1 L + Air 1 L) and F_VS 8% which yielded a respective F_AS of 1, 1.5, 2, 2.5, 3, and 3.5% at 1, 1.5, 2, 3, 3.5, and 4.5 min when used with N_2O and at 1, 1.5, 2, 3, 4, and 5 min when used with air.

In a test lung model study Jakobsson et. al.[4] reported wash-in with a respective FGF of 0.3 and 4 $L \cdot min^{-1}$ and a F_VS of 8%. They found that the F_AS reached 1 MAC (2.1%) at 547 ± 83 and 38 ± 6 s, respectively. It was possible to increase the AA concentration from 0 to 1 MAC value in around one minute by using a FGF of 4–4.8 L/min using a fixed dial setting of 3 MAC, but raising the FGF further did not result in shorter wash-in times. Wash-in times were significantly faster with higher flow rates for FGF spanning from 1, 2 and 4 L/min, however a plateau started at FGF 4–4.8 L/min, where increasing the FGF further up to 6 or 8 L/min did not shorten the time to reach 1 MAC significantly.[13]

The conventional method which uses initial high FGF during the wash-in phase defeats the purpose of LFA such as conservation of gases, reduced environmental pollution and economical savings even

though it provides a more stable gas composition within the breathing system. Beginning of anaesthesia is also a task-intense phase requiring multiple tasks to be performed to ensure the patient safety. Any additional tasks during this phase may have high chances of being forgotten with a potential for compromised patient safety. Therefore, the technique has to be simple to execute. We wish to evaluate a technique of initiating Sevoflurane LFA which is simple, has a quick wash-in and minimises gas consumption without compromising the safety when compared to conventional method of attaining LFA using initial high flows.

Methods

After obtaining the approval from the Institutional Ethics Committee of The Royal Hospital, Muscat, we will register this prospective, randomised, descriptive study in an appropriate online clinical trial registry. A written informed consent will be obtained from all the patients. Forty-eight patients of either gender aged 18-65 years, with American Society of Anesthesiologists (ASA) physical status of 1-2, undergoing elective surgery with the expected duration more than 1 hour under general anaesthesia requiring endotracheal intubation will be included. Pregnant women, smokers, patients with a body mass index (BMI) ≥30 kg/m_2, cardiac/pulmonary/renal or liver impairments, upper or lower respiratory infections within the past 6 weeks and anticipated difficult airway will be excluded.

Age, gender, height and weight of the patients will be recorded. All the patients will follow the standard fasting requirements and receive no sedative premedication. They will be randomised before entering the operating room into one of the two groups, 'conventional group' (Group C) and 'over-pressure group' (Group OP), using block randomisation technique with varying block sizes. An appropriate intravenous cannula will be secured in the operating room and Ringer's Lactate 500 ml will be started. The patients will receive standard anaesthetic care and intra-operative monitoring with electrocardiogram, pulse oximeter (SpO_2), non-invasive blood pressure (NIBP) and capnography. Avance CS_2 anaesthesia workstation (GE Healthcare, Madison, WI, USA) which has an integrated anaesthetic gas analyser, displays age-adjusted MAC according to the internal algorithm and returns sampled gas to the breathing system will be used in this study. The breathing system will consist of a 2 L reservoir bag, disposable breathing circuit, heat-moisture exchanger and standard circle system with Sodalime as the CO_2 absorbent. The workstation will be tested to ensure no leak in the system and vapourisers are calibrated.

Ideal Body Weight (IBW) of the patient will be calculated based on the following formula: IBW (kg)=50 + 0.91 (height in cm – 152.4) for Men and 45.5 + 0.91 (height in cm – 152.4) for Women. The ventilator will be preset in Pressure Control-Volume Guarantee (PCV-VG) mode with a tidal volume of 8 ml/kg of IBW, respiratory rate=14 breaths/min, positive end-expiratory pressure (PEEP)=5 cmH_2O and an inspiratory:expiratory ratio of 1:2. The set minute volume will be noted. The alarm for end-tidal Sevoflurane (F_AS) will be set at 2% to alert the clinician.

Heart rate (HR), blood pressure (BP) and peripheral oxygen saturation will be recorded before induction of anaesthesia, every minute until 5 min after induction and every 5 min intervals thereafter. The FGF will be set at 6 L/min with 100% O_2 during pre-oxygenation and manual ventilation. Following pre-oxygenation for 3 min, general anaesthesia will be induced with intravenous Fentanyl 2 μg/kg followed by Propofol 2 mg/kg administered over 30 seconds and Rocuronium 1 mg/kg for neuromuscular blockade. Lungs will be ventilated manually and propofol 20 mg every minute will be administered until tracheal intubation. Tracheal intubation with an appropriate size ETT will be performed 90 seconds later, the cuff inflated to 25-30 cmH_2O using a cuff-pressure monitor device and ETT secured with an adhesive tape. The correct ETT position will be confirmed by auscultation and square-wave capnograph. FGF will be paused during intubation and restarted after inflating the ETT cuff. The FGF hereafter will consist of O_2 and Air with a set F_IO_2=0.6. FGF and Sevoflurane vapouriser dial (F_VS) will be set as per the group allocation and mechanical ventilation will begin. The time of opening of vapouriser will be considered T_{zero}.

Following will be the steps during wash-in for achieving LFA:

The 'conventional' group (Group C): FGF will be set to 6 L/min and the F_VS 3% at T_{zero}. The FGF will be reduced to 0.5 L/min upon reaching F_AS 2%. Hereafter, the F_VS will be set to 4% and maintained till 15 min (T_{15}) from T_{zero}.

The 'over-pressure' group (Group OP): FGF will be set to 0.5 L/min and F_VS 8% at T_{zero}. Subsequently, the F_VS will be set to 4% upon reaching F_AS 2% and maintained till 15 min (T_{15}) from T_{zero}.

The time of reaching F_AS=2% will be noted in both the groups. The time taken in seconds from T_{zero} to reach F_AS 2% (T_{target}) will be calculated. Inspired concentration of Sevoflurane (F_IS), F_AS, and age-adjusted MAC will be retrieved from the automatically recorded 'trend' of parameters. F_IS, F_AS and age-adjusted MAC will be noted every 30 sec. starting from T_{zero}, till T_5 and every minute thereafter until T_{15}.

Consumption of gases (Oxygen, Air and Sevoflurane) from the beginning until T_{15} will be retrieved. Any reduction in mean BP >20% from the baseline will be treated with intravenous Ephedrine 12 mg bolus and consumption of Ephedrine will be noted. Expired minute volume (MV_E) at T_{target} and T_{15} will be noted. The study period will end at T_{15} in both the groups. Painting the surgical parts and draping will be permitted during the study period. Care will be taken to avoid any activity which risks ETT disconnection during the study period. Subsequent management of anaesthesia will be left to the discretion of the attending Anaesthesiologist.

For both the groups, 'stability of Sevoflurane concentration', defined as F_AS in the target range of 1.6-2.4% during the time interval from T_{target} till T_{15} will be assessed. The investigator will be allowed during this period to increase or decrease if needed the vapouriser dial by 1% at a time every 2 min to keep the F_AS in the target range. The number of times the vapouriser dial is adjusted will be noted. The system will be considered 'stable' if the F_AS is maintained in the target range without the need for dial adjustment and 'unstable' if vapouriser dial adjustment is needed at any time during this period.

Delivery of Oxygen will be monitored to ensure at least 300 ml/min and delivered F_IO_2 at least 0.3 at all time. The investigator will be allowed to increase if needed the set F_IO_2 by 0.1 at a time every 2 min to keep the delivered F_IO_2>0.3. The number of times the set F_IO_2 is adjusted will be noted. End-tidal carbon dioxide ($ETCO_2$) will be maintained between 30 and 40.

The aim of the study is to assess during the wash-in phase of LFA the feasibility of the method, stability of the system and consumption of gases. The primary outcome will be the time required to achieve F_AS 2%. Secondary outcomes will be the stability of the system assessed by the number of times vapouriser dial and the set F_IO_2 adjusted, consumption of gases and of ephedrine.

Statistical analysis

Sample size is calculated based on a previous study[8] which showed the 1-1-8 wash-in scheme with FGF=2L (O_2 1 L + Air 1 L) and Sevoflurane dial at 8% yielded an F_AS of 2% at 2 ± 0.5 min. Hence, we assume that with our wash-in technique using FGF=0.5 L (O_2 + Air) and F_VS 8% the time needed to reach F_AS=2% will be around 8 min. To detect a difference of 2 min (25%) with standard deviation (SD) of 2 using an alpha level of 0.05 and a power of 0.90 the sample size needed is 22 per group. For a possible 10% dropouts, it is decided to include 24 patients per group.

Statistical analysis will be carried out using an appropriate statistical software. Data will be presented as mean ± SD or median (range). Intergroup differences will be assessed for significance using Student's t, Kruskal-Wallis, chi-squared or Fisher exact tests, as appropriate. $P < 0.05$ will be considered statistically significant.

Study duration: Approximately 8 months (from December 2023 to July 2024). Data collection: December 2023-May 2024, statistical analysis and writing manuscript: June-July 2024.

How will the expenses be met with? : Does not involve any additional expenditure.

Department associated in the study: Department of Anaesthesia and Intensive Care, Royal Hospital, Muscat.

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