Low flow anaesthesia; cost-effectiveness of the Flow-I anaesthesia machine, a comparison to established anaesthesia delivery unit

VERSION V1.0

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Content

1. Protocol Summary

Title of study: Low fresh gas flow during elective general anaesthesia - A study comparing the Flow-I and a conventional anaesthetic machine with a circle system including a bellow reservoir.

Institution: Department of Anaesthesia & Intensive Care Danderyds University Hospital, Institution for Clinical Science, Karolinska Institutet, Stockholm, SWEDEN

Study time-lines: Patients inclusion in 8 month, study report in 12 month, from initiation of patient into study.

Objective: To test the hypothesis that the Flow I patient circle and fresh gas generation provides a faster and less gas consuming equilibrium and maintenance of general anaesthesia as compared to a conventional anaesthetic machine including a breathing circle with a below reservoir.

The study will compare Flow I to a conventional anaesthetic machine during routine elective general surgery in ASA 1-2 patients under general anaesthesia based on desflurane at a fresh gas flow of 1 L/min.

Study design: prospective, randomized study.

Participants: one hundred ASA 1-2 patients aged 20 – 60 years scheduled for elective general anaesthesia will be recruited. Patients will be randomized to Flow I or a conventional anaesthetic machine having general desflurane anaesthesia at a fresh gas flow of 1 l/min fresh gas flow.

Duration of treatment: Study protocol covers 72 hours after end of anaesthesia (follow-up of quality of recovery until day 3) .

Main measurements:
Time to go from 1 to 1.5 MAC end-tidal concentration during controlled ventilation with a tidal volume of 6 ml/kg and a respiratory rate of 12 breaths per minutes. Amount anaesthesia agent consumed; Gram inhaled anaesthetic per minute anaesthesia.

2. Background

Desflurane, one of the third generation of inhaled halogenated anaesthetics has physiochemical properties promoting its use in low flow anaesthesia. The low blood and tissue solubility promotes its rapid equilibration and thus potential benefit when used in conjunction with lowering of the fresh gas flow. It has been shown superior to isoflurane for control of haemodynamic also at flow rates of 1 L/min.

Bennett et al compared desflurane and isoflurane for control of haemodynamic response. They found that Desflurane allowed for more rapid control of blood pressure response to surgical stimulus median 2 minutes (range 1 to 12 minutes) for desflurane versus 6 minutes (range 1 to 12 minutes, $p = 0.011$). The desflurane group required fewer 30% incremental anaesthetic increases than the isoflurane group (1.8 versus 2.5, $p = 0.016$) to control increased systolic blood pressure. End tidal/inspired drug concentration ratios were closer to unity in the desflurane patients both before (0.94 versus 0.80) and after (0.86 versus 0.70) changes in drug concentration to treat increased systolic blood pressure.

Avramov et al evaluated the effect of the fresh gas flow (FGF) rate and the anesthetic technique on the ability to control the acute hyperdynamic response to a specific surgical stimulus during surgery in 90 consenting ASA physical status I-III patients undergoing lower abdominal procedures. The patients were initially maintained with desflurane or isoflurane, 0.7 minimum alveolar anaesthetic concentrations, at total FGF rates of either 1 or 3 L/min. In response to the surgical stimulation of skin incision and retropubic dissection, an increase in mean arterial pressure (MAP) ~20% above the pre-incision baseline MAP value provoked a stepwise increase in the inspired concentration of the volatile anaesthetic or the IV administration of a variable-rate infusion of esmolol. They found that desflurane was significantly faster in controlling haemodynamic response to painful stimulation also at low, 1 L/min fresh gas flow. At 1 L/min, the average time to control the mean arterial pressure was significantly shorter with desflurane (17 ± 12 min) compared with isoflurane (29 ± 16 min), with 60% of the patients in the isoflurane group requiring rescue therapy.

Low blood gas solubility promotes in theory the use of the third generation inhaled anaesthetics for use during general anaesthesia with low fresh gas flow. The benefits of low blood and tissue solubility during low and minimal flow are not yet studied.

Reducing the fresh gas flow has many benefits, it reduces the risk for unnecessary work place contamination, it reduces the environmental pollution and it is cost-effective . Many institutions are therefore adopting low flow technique. Inhaled anaesthesia with low flow technique may also have benefits as compared to the intravenous anaesthetic technique, propofol based anaesthesia that has become increasingly popular. The low flow inhaled anaesthesia technique would assumingly become cost-effective also with the availability of generic low prize propofol . The easiness to start and continuously monitor end-tidal concentration should also be recognised.

Choi et al compared two fresh gas flows techniques and the time to effect: control of a blood pressure increase during surgery with sevoflurane. They compared the ability of the Zeus

multifunctional anaesthesia system to control haemodynamic response to surgical stimulation in semi-closed anaesthesia (SCA) or closed circuit anaesthesia (CCA) modes. Fifty patients undergoing gynaecological surgery were randomly assigned to SCA or CCA. Anaesthesia was induced with 2 mg/kg propofol and paralysis was achieved with 0.9 mg/kg rocuronium, i.v. and maintenance was with sevoflurane (minimum alveolar concentration [MAC], 1.0) using 2 l/min oxygen plus 2 l/min nitrous oxide (SCA 4 l/min group) or 50% oxygen plus 50% nitrous oxide (CCA group). An increase in mean arterial pressure (MAP) > 20% above baseline in response to surgical stimulation provoked a stepwise increase in sevoflurane (1.3 MAC and then 1.6 MAC), followed by fentanyl 1 pg/kg intravenously (rescue drug). The time required for MAP to return to within 10% of baseline was significantly shorter in the CCA group (6.4 +/- 3.6 min) compared with the SCA 4 l/min group (10.2 +/- 6.0 min). It seems reasonable to conclude that time to onset of effect of sevoflurane is rapid and dependent on the dose administered.

The breathing circle should ascertain an adequate gas mixture inhaled; oxygen and inhaled agent as well as absence of carbon dioxide. The anaesthetic machine provide the fresh gas entering the breathing circle. There are technical developments. The delivery of fresh gas differs between devices.

Objective

To test the hypothesis that the Flow I breathing circle system without a below reservoir provides a faster and less anaesthetic vapour consuming wash-in and maintenance of $Et_{desflurane}$

The aim of the study is to compare gas kinetics, time needed in order to change the end-tidal concentration, and vapour consumption (and associated cost) between the novel Flow-I circle system and the standard anaesthesia equipment/machine at the centre (multi-centre study; 3 centres) during general anaesthesia for routine elective surgery in ASA 1-2 patients.

The study will compare The Flow I to a conventional anaesthetic machine including a breathing circle based on a below reservoir during routine desflurane with a fresh gas flow of 1 L/min in ASA 1-2 patients having elective surgery.

3. Inclusion and Exclusion Criteria

100 ASA 1-2 patients aged 20 – 60 years scheduled for elective general anaesthesia will be recruited.

Inclusion criteria

- Age 20 to 60 years
- BMI 20-30
- ASA 1-2

Exclusion criteria

- COPD
- BMI > 30
- ASA >2
- Sever cardiovascular disease ASA >2
- Renal disease
- Diabetes
- Hepatic disease
- Psychiatric disease or any psychoactive medication

All patients will receive all treatment and care in accordance to the routines of the department apart from the volatile anaesthetic and fresh-gas flow that the patient is randomised to.

All study specific data will be recorded and collected on a Case Record Form coded in accordance to randomisation.

4. Ethics Committee Approval and Patient Informed Consent

The study will be reviewed by regional Ethics Review Board. The protocol will be reviewed by registered in Clinical Trial Data bases in accordance to National Regulations

The study will not be initiated before approval has been received from the Ethics Review Board and reviewed by National drug authority as needed.

All patients will receive verbal and written information and signed informed consent will be required before any patients are entered into the study.

5. Randomisation

Patients will be randomised on entering the operating theatre. The anaesthetist responsible for the patient will open an envelope in which the group will be noted. Each patient will have an inclusion number and each inclusion number will correspond to attribution to a treatment group in accordance with a randomization list pre-established by the envelope technique. The envelopes will be created from 2 random lists.

Patients will be randomised to

- Flow I
- Conventional anaesthetic machine

for maintenance of anaesthesia.

and subsequently to a fresh gas flow of

- 1 L/min FiO2 0.5 oxygen in air

6. Anaesthesia Protocol

All patients will follow the routines of the department expect for the randomisation of anaesthetic machine

All patients will receive general anaesthesia in accordance to local practice expect for the randomisation of anaesthetic machine and maintenance of a fresh gas flow of 1 L/min during anaesthesia.

- Establishment of intravenous access, 1000 ml Ringeractetat.
- All patients will have preoxygenation FiO2 0.8 for 60 seconds including 3 “deep breath” prior to propofol (2.5 mg/kg) fentanyl (2 microgr/kg) co-induction will be administered until adequately anaesthetised.
- Intravenous continuous infusion remifentanil will be administered in a dose 3 µg/ml
- Muscle relaxation will be administer in accordance to local practice
- Patients will be ventilated with oxygen for 3 minutes and thereafter intubated.

No surgery will commence until a 1.5 MAC is reached.

The vaporizer will be weighed before and after each patient anaesthetised and gram inhaled anaesthesia per minute anaesthesia will be calculated

The fresh gas flow is increased to 4 L/min oxygen and 2 L/min air when last stitch is made.

- Time to extubation
- Time to state name and date of birth
- Time to discharge from the PACU

All patients will receive PONV prophylaxis in accordance to local routines.

- PONV during the first 24 hours after surgery
- Patients satisfaction

7. Outcome Variables

Primary study variable, amount of gas vaporized halogenated anaesthetic per minute anaesthesia.

Secondary study variables;

1. Time needed to increase from Etaa 1 to Etaa 1.5 age adjusted MAC with a constant 1 L/min. and a dialled 3 MAC, the vaporiser set at 18 %, in conjunction to start of surgery
    a. When the 1.5 Etaa has been achieved the gas setting should be adjusted in accordance to clinical needs throughout the surgery.
2. Time needed during wash-out, time from cessation of administration until reaching 0.2 MAC
    a. Time from cessation of administration to awakening; extubation and able to state name and date of birth
    a. Time to reach Aldrete > 8
    b. Pain and need for analgesics and anti-emetics during the PACU stay
    c. Follow-up of quality of recovery PQRS

8. Statistics

As this is an explorative pilot study thus no formal sample size will be determined.

Power calculation

Based on the experience from pilot study a vaporizer consumption of 0.28 gr/min with a SD of 0.07 and the Flow-I being more efficient vapor injection providing an estimated 0.03 gr/min reduction of vapor a group size of 43 patients would be required in order to verify a significant difference $p < 0.05$ at a power of 80%. A total of 2 x 43 in all 86 and a drop out / lost for follow-up of about 10-14 patients 100 patients will be recruited.

Comparison of normally distributed variables will be done by Student's t-test, of variables not following a normal distribution by Wilcoxon Test.

9. Study Timelines

Total duration of the study: Estimated 12 months from start of patient inclusion until study report

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10. Insurance

All treatments except randomisation will be given in accordance to the routines of the department. No extra insurance is therefore required. The National Patient Safety Insurance will cover potential insurance claims.

11. Confidentiality

All retrieved data will be compiled on CRFs identified by the randomisation code. Patient identity will only be available in case of adverse effect or required by any other reason for the medical care. The patient code list will be stored in a dedicated storage place, patient record storage and available 24 hours 7 days a week after contact with Principal Investigator.

12. Adverse Event Reporting

All serious adverse effects and adverse effects or risks with respect to the study material will be reported in accordance with the applicable local and European Union laws and regulations. Regulatory Authorities, Ethics Committees and all participating investigators are informed in accordance with the given timelines set out in the applicable laws and regulations.

The investigator will also notify all serious adverse events or other significant safety concerns irrespective of causality that arise to Maquet within 24 hours,

13. References

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