colleagues published a newer checklist for cost-effectiveness analyses in global surgery in 2017.[10]

Conclusions

High-quality, double-blind RCTs, such as the PREVENTT trial, are the highest standard for determining effectiveness of various medical and surgical interventions and can help define standards of care. Economic considerations must also be taken into account when making health policy decisions. Cost-effectiveness analysis is a critical tool, and maximising reproducibility of these calculations using standardised techniques and verifying with existing checklists will allow for the highest standard in data-driven policymaking for population-based healthcare delivery.

Declarations of interest

The author declares that they have no conflict of interest.

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Desflurane in modern anaesthetic practice: walking on thin ice(caps)?

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The third-generation volatile anaesthetic agents desflurane and sevoflurane were introduced into clinical practice in the 1990s in response to the perceived need for rapid return of consciousness after ambulatory surgery.[1] Initially marketed by two competing pharmaceutical companies, their relative merits have been debated for three decades.[2] Of the two, desflurane has a lower solubility in blood and therefore the fastest offset, providing a rapid emergence, which is more notable in obese patients and after prolonged anaesthesia.[2] Furthermore, some authorities (including the US Food and Drug Administration [FDA]) have deemed desflurane to be more suitable than sevoflurane for low-flow anaesthesia, as it undergoes only negligible metabolism and minimal reaction with soda lime.[3] However, desflurane has several well-known disadvantages, including a pungent odour (making it a respiratory irritant), lower potency, and environmental impacts related to its manufacture, administration, and discharge into the atmosphere, calling into question its continued use as a general anaesthetic agent.[1,2,4,5]

Clinical impacts of desflurane

TIVA and regional anaesthesia are becoming increasingly popular for environmental and clinical reasons, with regional anaesthesia advocated preferentially during the current coronavirus crisis to preserve drug stocks and avoid aerosol-generating procedures.[6,7] However, national studies suggest that the most common method of delivering general anaesthesia involves intravenous induction and inhalation maintenance.[6,8] Mainly historical data indicate that the faster elimination desflurane from the body facilitates rapid-turnover operating lists and may benefit some higher-risk patients, but there is scant clinical evidence to confirm these benefits in current anaesthetic practice. A recent observational study of more than 100 000 cases by Zucco and colleagues,[9] for example found no difference in postoperative pulmonary complications between patients anaesthetised with sevoflurane and desflurane when adjusted for confounding factors.

One potential advantage of desflurane is the faster time to recovery of consciousness and tracheal extubation. However, although meta-analyses of RCTs have confirmed that this is a consistent statistically significant finding (Table 1), the magnitude of the effect is minimal (only a few minutes in most circumstances), and it does not appear that this translates to shorter patient stays in the PACU.[9–13,15] Furthermore, as pointed out by Macario and colleagues,[11] because RCT study protocols tend to require the use of a constant concentration of general anaesthetic agent up to the point of wound closure, the common clinical practice of tapering the anaesthetic dose as the surgical stimulus reduces is not represented, and this may further reduce any 'real world' difference between agents. We contend that a trivially more rapid emergence from general anaesthesia with desflurane compared with sevoflurane may be of greater promotional benefit to the manufacturer than either clinical benefit to the patient or organisational benefit to surgical operating efficiency.

Although previous studies of desflurane have been concerned with its pharmacokinetic qualities, in the current issue of the *British Journal of Anaesthesia*, Ryu and colleagues[16] focus on an important *pharmacodynamic* difference between volatile agents. In this meticulously controlled study, participants who were scheduled for arthroscopic knee surgery were randomised to receive an additional 35 min of anaesthesia before their operation with one minimum alveolar concentration (MAC) of either sevoflurane or desflurane, after a target-

Table 1 Meta-analyses of RCTs comparing time with emergence, tracheal extubation and PACU discharge of patients anaesthetised with desflurane, sevoflurane, or propofol TIVA. *Removal of supraglottic airway. NS, not significant; NR, not reported; PONV, postoperative nausea and vomiting.

Study	Context	Desflurane *vs* sevoflurane			Desflurane *vs* propofol			Notes
		Emergence (min)	Extubation (min)	PACU discharge (min)	Emergence (min)	Extubation (min)	PACU discharge (min)	
Gupta and colleagues[10]	Adult patients. Ambulatory surgery	−<1	−<1	+6	−1.3	NR	NR	Less PONV in propofol group.
Macario and colleagues[11]	Adult and paediatric patients. Ambulatory and inpatient surgery	−1.7	−1.3	NS	NR	NR	NR	No difference in PONV between groups.
Liu and colleagues[12]	Patients with BMI >30 kg m^{-2}. Ambulatory and inpatient surgery	−3.1	−3.9	+1.28	−10.7	−13.2	NR	No difference in PONV or analgesic requirement between groups.
Stevanovic and colleagues[13]	Adult patients. Laryngeal mask airway	−3.8	−0.7*	NR	NR	NR	NR	No difference in cough or laryngospasm between groups.
Lim and colleagues[14]	Paediatric patients. Ambulatory surgery.	−2.7	−2.2	NR	NR	NR	NR	No difference in incidence or severity of emergence agitation between groups.
Guo and colleagues[15]	Paediatric patients. Ambulatory and inpatient surgery	NS	−3.3	NS	NS	−3.83	NS	No difference in PONV or analgesic requirement between groups. Less emergence agitation with propofol *vs* desflurane or sevoflurane.

controlled induction with propofol and muscle relaxation with rocuronium. Perfusion index (a measure of peripheral perfusion derived from the pulse oximeter signal), MAP, and heart rate were recorded every minute throughout the study period, which included a standardised noxious stimulus (tetany from a peripheral nerve stimulator) after 30 min of vaporiser adjustment and equilibration time. The desflurane group showed a significantly higher perfusion index (indicating inferior peripheral perfusion) and a significantly lower MAP than the sevoflurane group. These findings, the authors suggest, indicate that desflurane has more potent vasodilatory properties than sevoflurane at an equivalent dose, at a magnitude that may be associated with harm.[16]

Intraoperative hypotension is associated with adverse patient outcomes including mortality, acute kidney injury, myocardial infarction, and wound infection in settings including orthopaedic trauma, vascular, thoracic, and general surgery.[17–20] Concerningly, these are all surgical specialties in which high-risk and prolonged operations are relatively commonplace and therefore the use of desflurane may be most tempting for clinicians. A survey of UK practice indicates that desflurane appears to be more commonly used in older patients, who are at higher risk of the complications of hypotension.[8] The mean pre-stimulation MAP in Ryu and colleagues' desflurane group was 73 mm Hg, compared with 81 mm Hg in the sevoflurane group.[16] Although one MAC of volatile agent is arguably a higher dose of anaesthetic than was required given the lack of 'surgical' stimulation, these findings do have potential clinical significance. A recent systematic review by Wesselink and colleagues[21] concluded that the risk of end-organ injury begins to increase at a MAP of <80 mm Hg for a duration >10 min. Although it cannot be determined if the (comparatively young and fit) participants in the study by Ryu and colleagues[16] came to any harm, as patient outcomes were not assessed, this is a potentially important signal and requires further investigation in older and more comorbid populations.

Environmental impacts of volatile anaesthetic agents

The environmental effects of inhaled anaesthetic agents were recognised before the introduction of sevoflurane and desflurane, although early focus was on the potential for chloride ions liberated by the ultraviolet photolysis of agents such as isoflurane (but not sevoflurane or desflurane) to contribute to the destruction of the ozone layer.[1] Subsequently, attention has focused on the action of inhaled agents as 'greenhouse gases',[5,22–24] contributing to anthropogenic global warming through radiative forcing, that is the absorption of infrared radiation that would otherwise escape into space. The degree to which a substance released into the atmosphere contributes to global warming depends on two factors: firstly the radiative efficiency, the amount of infrared radiation absorbed, which is determined by the number and type of atomic bonds within the structure of the molecule; and secondly whether there are any naturally occurring molecules (e.g. water vapour) that would otherwise absorb infrared radiation at the same wavelengths.[5,23]

The global warming potential (GWP) of greenhouse gases differs over time, depending on the lifespan of the molecule, with more atmospherically persistent molecules having a greater cumulative impact. The GWP_{20} and GWP_{100} express the GWP of a substance over 20 and 100 yr, respectively, in comparison with the effect of an equal mass of carbon dioxide. In anaesthetic practice, the differences in molecular mass and potency between volatile agents can make comparison on the basis of GWP challenging. The concept of carbon dioxide equivalencies (CDE) addresses this issue by multiplying the GWP by the mass of anaesthetic agent used per hour at a given MAC and fresh gas flow (Table 2), thereby enabling a clinically relevant comparison.[23]

Although sevoflurane is generally considered to be the least damaging volatile anaesthetic from a climate change perspective, life cycle analysis has shown that its GWP_{100} is about 3 orders of magnitude greater than an equivalent dose of propofol TIVA.[4] It is for this reason that the National Health Service Sustainable Development Unit has designated volatile anaesthetic agents, and desflurane in particular, to be a 'carbon hotspot'.[24] The difference between the GWP of anaesthetic agents is more pronounced at 100 yr than at closer time horizons, owing to the greater environmental persistence of desflurane. This raises the question of what time horizon should be used when making policy and practice decisions. Recently, it has been suggested that the 20 and 100 yr time horizons underplay the atmospheric effects of volatile agents in the face of a pressing climate crisis, because their global warming effects will remain at their atmospheric release levels if their use continues unabated.[23] Regardless of their comparative environmental impacts, *both* desflurane and sevoflurane have profound global warming impacts, such that anaesthetists need to consider seriously the default use of volatile agents for general anaesthesia.[22]

Desflurane: a 'triple bottom line' approach

Desflurane, then, has little evidence of important patient benefit, considerable environmental impacts at a time of climate crisis, and now appears to have evidence of potential for harm.[4,9–16] Given these widespread drawbacks, anaesthetists have to question the rationale for its continued use. As with any practice, the risks and benefits associated with desflurane use can be conceptualised using the so-called 'triple bottom line' approach by considering impacts on 'people' (e.g.

Table 2 Global warming potential (GWP) of sevoflurane and desflurane, at 1, 20, and 100 yr, and corresponding carbon dioxide equivalents (CDE) per hour of anaesthesia at 1 MAC and 0.5 L min^{-1} fresh gas flow. One hour of desflurane use at 1 MAC and 0.5 L min^{-1} fresh gas flow has a GWP_{100} equivalent to 22.42 kg CO_2. This is comparable with driving 90 miles in a typical UK family car, and more than 20 times greater than if sevoflurane were used. Data adapted from Özelsel and colleagues.[22]

	GWP_1	CDE_1 (kg h^{-1})	GWP_{20}	CDE_{20} (kg h^{-1})	GWP_{100}	CDE_{100} (kg h^{-1})
Sevoflurane	4285	21.43	796	3.980	216	1.08
Desflurane	8526	107.45	5513	69.49	1778	22.42

the patient, staff members, and broader society), 'planet' (i.e. environmental sustainability) and the 'public purse' (i.e. healthcare finances).[5,25]

People

Arguably, the most important element of decision-making in anaesthetic practice relates to patient safety. Here, there is little evidence of any benefit to desflurane, and the degree of hypotension demonstrated by Ryu and colleagues[16] is a cause for concern, particularly in older or comorbid patients.[9–16] In terms of quality of care, desflurane is consistently associated with more rapid emergence from anaesthesia and tracheal extubation, however these benefits are small in magnitude and do not lead to any improvement in discharge times.[9–13,15] As a consequence, these benefits are likely to be noticed only by the anaesthetic team, but not by the patient or operating theatre staff more generally. Although patient outcomes are of paramount importance for the anaesthetist, this does not mean that the effects of climate change on communities worldwide should be discounted.[25]

Planet

Depending on the time horizon used, the GWP of desflurane is 5–20 times more than that of sevoflurane.[4] Although technologies to capture and reprocess desflurane have been developed and are currently being trialled in some healthcare institutions, these would have to be exceptionally efficient to overcome this magnitude of difference.[5,22,25] Although sevoflurane is not licensed for low-flow anaesthesia in some countries despite evidence of the safety of this technique, even at fresh gas flows of 1–2 L min^{-1} it remains markedly less environmentally harmful than low-flow desflurane in terms of potential for climate change.[3,4] Furthermore, evidence supports the preferential use of total intravenous, or regional, compared with inhalational, anaesthesia in limiting the potential climate impacts of anaesthetic practice.[4,5,7,22,24]

Public purse

Desflurane is about one-third the potency of sevoflurane and, although it was initially less expensive whilst 'on patent', it is now typically more costly owing to the market forces created by the wider availability of generic sevoflurane (240 ml desflurane ~£90, 250 ml sevoflurane ~£60; personal communication).[1] Even accounting for the negligible metabolism and low solubility of desflurane, and its (minor) benefits in the speed of early recovery from anaesthesia, at an equal fresh gas flow and MAC desflurane has consistently been found to be more expensive than sevoflurane.[26] Therefore, it is only in countries where sevoflurane is unlicensed for low-flow anaesthesia that a cost-effectiveness argument could be made in favour of desflurane.[3] It should be noted however, that the additional non-drug costs to healthcare institutions (e.g. heating the desflurane vaporiser) and public finances more broadly (e.g. as a consequence of global warming) are not accounted for in existing cost analyses.

In conclusion, anaesthetists have a responsibility not only to care for the patient in front of them, but also to safeguard the health and welfare of future generations.[22,25] The study by Ryu and colleagues[16] in this issue of the *British Journal of Anaesthesia* adds to existing evidence aligning these two responsibilities through the discontinuation of desflurane use and manufacture.[9,16] Individual anaesthetists, and the wider profession, can choose how to deliver general anaesthesia. We accept that inhalational anaesthetic agents may be appropriate in certain circumstances, but assumptions about the specific clinical benefits of desflurane based on its physiochemical properties are breaking down. In our opinion, the arguments against its use are now overwhelming. We strongly encourage anaesthetists who are still using desflurane to reconsider the evidence for its use, and ask themselves how they might transition to using less environmentally harmful alternatives.

Authors' contributions

All authors conceived, wrote, and edited the manuscript.

Declarations of interest

CS is a former member of the editorial board of *BJA Education*. The authors declare no other conflicts of interest.

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Mast cell activation tests: a new tool in the investigation of suspected perioperative allergic reactions?

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With deaths attributable to anaesthesia estimated to range from 1:125 000 to 1:180 000 anaesthetics,[1–3] there has been focus on the development of safety management systems to prevent avoidable deaths.[4,5] If we want to continue to improve anaesthesia outcomes and safety, then we must also focus on the diagnosis and treatment of rare, but potentially life-threatening perioperative events that account for an increasing proportion of adverse outcomes.[6] In this regard, immediate hypersensitivity reactions remain a major concern for anaesthesiologists with a mortality of ~4%.[7,8] In this issue of the *British Journal of Anaesthesia*, Elst and

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