Brief Communication

Nitrous oxide and the Eye

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Fewer anaesthetists seem to be using nitrous oxide (N_2O) off late, presumably due to a combination of factors such as reported side effects, concern for environment and availability of newer agents.[1] However, a recent review concluded that it is not yet time to abandon it completely due to emerging evidence for newer applications as also better understanding of its benefits and risks.[2] Concerns about its use in ophthalmic anaesthesia mostly stem from fear of causing adverse effects due to postoperative nausea and vomiting (PONV) and intraocular pressure (IOP) issues. This brief report will look at the relevant evidence and attempt to make recommendations.

There are three main scenarios where N_2O is of relevance to the eye in discussions relating to general anaesthesia (GA):

- Ophthalmic procedures not involving insertion of intraocular gas (IOG)
- Ophthalmic procedures involving IOG
- Non-ophthalmic procedures in the first three months following an eye procedure.

1) Ophthalmic procedures not involving IOG: These procedures can involve any part of the eye including lens, cornea, extra-ocular muscles, as also for glaucoma, dacryocystorhinostomy, oculoplastic etc. Majority of these are done under local anaesthesia but certain groups of patients need GA. N_2O itself does not seem to affect the IOP much. IOP increased by a maximum of 2.4 mmHg from baseline in healthy volunteers when N_2O was administered.[3] Of interest, nitric oxide plays an important role in lowering / regulating IOP and is the subject of recent research.[4] Due to its low solubility, N_2O contributes to the 'second gas effect' leading to faster induction and improved arterial oxygenation compared to a combination of oxygen and air.[2] This is useful for inhalational induction of anaesthesia especially in children where rapid induction is desirable. N_2O has 'MAC-sparing properties' which allows lower concentration of volatile agents, improved haemodynamic properties and decreased risk of respiratory depression.[5]

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Article History
Received: 9th November 2020
Revision: 14th November 2020
Accepted: 1st December 2020
Published: 14th January 2021

How to cite this article: Nitrous oxide and the Eye. Santhana Kannan. Indian J Ophthal Anaesth 2021;01;01:34-40

As a high proportion of patients undergoing ophthalmic surgery have systemic co-morbidities, this property is very useful. N_2O allows faster emergence from anaesthesia due to its short context-sensitive elimination half-life and reverse 'second gas effect' when inhaled volatile agent is stopped.[2] PONV is not an issue if the duration of exposure is less than 75 minutes and when pharmacological prophylaxis is used.[6]

Nevertheless, it may be prudent to avoid N_2O for certain procedures known to be associated with increased incidence of PONV such as strabismus repair. N_2O is a greenhouse gas and can contribute to ozone depletion. Although medical use of N_2O is estimated to represent < 1% of global N_2O pollution, routine use of low flow anaesthesia will further reduce this.[7] Due to its multiple advantages, for the majority of procedures not involving IOG, N_2O can be safely used for general anaesthesia.

2) Ophthalmic procedures involving IOG: IOG is used as a tamponade agent in vitreo-retinal surgery such as retinal detachment and macular hole repair. Following intravitreal administration, gas surface tension holds the retina against the choroid allowing retinal pigment epithelial pump to remove sub-retinal fluid and aid healing of the retinal breaks. IOG is also being used in endothelial keratoplasties (lamellar corneal grafts) either during the initial procedure or for "re-bubbling" dislocated grafts. The gases used in all of the above context include sulphur hexafluoride (Sf6), perfluoroethane (C2F6) or perfluoropropane (C3F8). They differ in their physical properties including expansibility, concentration and time taken to get reabsorbed. Any injected gas needs to stay in the eye for at least twelve days to aid effective healing.[8] Air alone is not used anymore as it tends to get reabsorbed by about a week and does not last long enough. An IOG bubble injected during surgery typically consists of a mixture of air and one of the other gases.

Mostafa et al found that when nitrous oxide is used in the setting of an air bubble in eye, the IOP rose steadily over the first few minutes to a peak level which was 18-20 mm Hg above the baseline.[9]

Thereafter no further rises occurred, but gas bubbles were noted to be escaping from the sclerostomy sites. Towards the end of surgical procedure, the IOP was frequently observed to return towards the baseline level. They considered that per-operative rise in IOP secondary to N_2O movement (when air is used as IOG) are not of significance in vitrectomy because of the venting effect of the sclerostomies. However, they recommended that N_2O be discontinued prior to air injection due to potential for globe hypotony at the end of procedure. Indeed, it has been shown in an animal study that the cornea tends to become concave due to rapid efflux of N_2O.[10]

N_2O is 117 times more soluble than SF6. When SF6 is injected into the vitreous cavity, the more soluble N_2O present in the

surrounding blood and tissues diffuses into the bubble faster than SF6 diffuses out.[11] Almost threefold increase in volume of the injected SF6 bubble has been estimated when 70 per cent N_2O is administered, with only minor increases if N2O is discontinued prior to injection.[12] If N_2O is added following SF6 intravitreal injection, the IOP increases significantly.[13] However, in a later study, Briggs et al observed that at 24 hours, there was no difference in size of gas bubble (C3F8) with or without N_2O.[14] The postoperative IOP at 20 minutes was raised in 50% of patients in non-N_2O group and 44% of patients in N_2O group. It was postulated that uncontrolled leakage from the sclerostomies was the most likely reason. It is to be noted that those days, 20 G needles were used for sclerostomies compared to 25 or even 27 G needles today. Hence, the leakage is likely to be much lower. Manufacturer information warns that the use of N_2O must be stopped at least ten minutes prior to gas injection.

With the advent of remifentanil, there is not a huge justification of continuing to use N_2O in vitreo-retinal surgery. In patients with limited systemic reserve requiring general anaesthesia for vitreo-retinal procedures, a local anaesthetic block prior to surgical incision will allow smaller doses of general anaesthesia agents and minimise adverse haemodynamic effects.[15] In procedures involving IOG, it would be best to avoid N_2O.

3) Non-ophthalmic procedures following a recent eye procedure: IOG vary in their degree of expansion and time taken to disappear from the eye is directly proportional to this. For example, SF6 remains in the eye for two weeks whereas C3F8 can be present for two months. Gas expansion may cause increased IOP in four circumstances: high altitude, influx of N_2O, excessive concentration of IOG, and decreased aqueous drainage through the trabecular meshwork.[16] If N_2O is inhaled (either for analgesia, anaesthesia or use as a recreational drug), influx into this gas bubble (similar to closed air spaces) can cause acute increase in IOP with potential for blindness due to retinal ischaemia.[17]

Study in cats showed that when SF6 is the IOG, the bubble volume increases 300% with N_2O and 50% with air. Hence, even when N_2O is avoided, there is some increase in the IOG volume.[18] In the presence of SF6, IOP could rise by 100% during N_2O anaesthesia within 24 min.[19] A more than threefold volume increase may be seen over 1 hour of N_2O use, which is sufficient to occlude the central retinal artery blood flow.[20]

Duration of administration of N_2O as also the size of IOG bubble at the time are important determinants of degree of damage.

If a patient had SF6 12 days ago, the size of the residual bubble would be small leading to reduced magnitude of increase in IOP by N_2O. The longest reported duration between a retinal procedure with IOG and subsequent

visual loss from N_2O anaesthesia is 41 days.[21] Irreversible damage to retina can happen after 100 minutes of ischaemia.[22] It is recommended that N_2O be avoided for 3 months in patients who had IOG. This blanket rule is necessary as it may be difficult to know the exact gas patient had in the eye and the benefits of avoiding N_2O outweigh the risks.

Preoperative assessment must include details about any recent procedure involving the eye. Patients may not necessarily feel that the eye procedure done a few weeks ago is relevant. Hence the nature and timing of past surgical procedures must be specifically questioned. Certain episodes of IOG instillation are done in outpatient setting in some centres which the patients may not deem as a 'surgical procedure'. The risk increases significantly when patient is unable to give a history due to decreased consciousness or lack of mental capacity. If there is doubt, N_2O must be avoided. To aid safety, patients are now being issued with wristbands with relevant advice. The Royal College of Ophthalmologists issued a safety alert in Dec 2018.[23]

There is a theoretical risk of harm (raised IOP or hypoxic iris) in anterior chamber gas bubbles during keratoplasty in the same circumstances such as flying, high altitude or N_2O use. It is currently unclear at present whether this represents a significant risk but patients are being warned against flying postoperatively. If N_2O is inadvertently given to a patient with IOG and is recognized intraoperatively, immediate steps should be taken.[24] N_2O should be ceased immediately and 100% oxygen should be administered. Oxygen has been shown to lead to faster reversal of bubble expansion than air alone. Ophthalmology consultation should be sought. If ophthalmologist is not available, and the eye feels hard to palpation after 5 minutes of stopping N_2O (using other eye for comparison), then consideration of pars plana paracentesis should be given to vent excess gas from the eye. The principle is similar to needle thoracostomy for relieving tension pneumothorax except that the needle can be removed once the globe is decompressed. There is no risk of continued influx of N_2O if it has been stopped.

Using a short (1/2 inch) needle (26 – 30 G), pierce the sclera of the eye 4 - 5 mm from the limbus (junction between clear cornea and white sclera, see Figure 1.

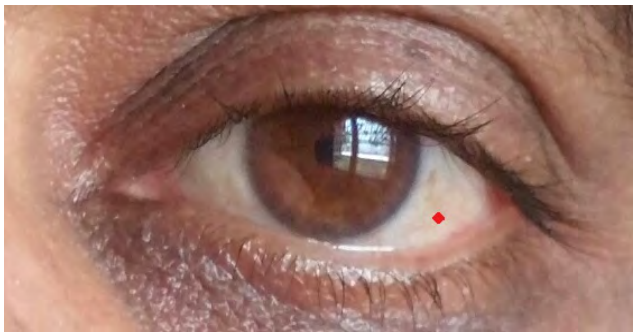

Figure 1. The red dot represents the area for needle puncture for the pars plana paracentesis.

The needle should be directed perpendicularly toward the centre of the eye. A few seconds is typically enough to reduce IOP to safe pressures and removal of a precise amount is not essential. The sclera is only 1 mm thick and hence the needle need not be inserted too deep to enter the globe.

It is essential to be away from limbus to prevent damage to the aqueous draining mechanisms and lens. However, being too far away from the limbus carries the risk of inadvertent retinal damage. Vitreoretinal surgeons insert needles for procedures and usually use a calliper to measure the distance. Due to potential for damage, it is recommended that this procedure is preferably done by an ophthalmologist (or someone who has done intravitreal injections before). It will take more than half an hour for sufficient N_2O to diffuse into IOG bubble. Hence, just because N_2O has been given for half an hour is not an automatic indication for pars plana paracentesis. There must be evidence of raised IOP.

In summary, N_2O is a useful adjunctive general anaesthetic agent for use in most eye procedures not involving insertion / presence of gas bubble. The only exception could be strabismus surgery where the potential risk of PONV is higher. For procedures involving gas bubble, it is best avoided and other agents such as remifentanil should be considered. In patients who have undergone a procedure in the eye within the last three months, the potential for presence of gas bubble must be considered. Wider availability and routine use of 'alert wristbands' should help in eliminating the risk of avoidable blindness due to use of N_2O. When N_2O is used, low flow anaesthesia should be used where possible.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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