

CHALLENGES IN ANAESTHESIA DURING SPACE EXPLORATION MISSIONS

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ABSTRACT

Aim

NASA and private spacefaring companies plan to send exploration missions to Mars within the next two decades. The environment of space, duration of the mission, distance from Earth, and limited available resources present significant challenges for the provision of health care. It has been estimated that at least one medical emergency is likely to occur during such a mission, which may necessitate surgical treatment, and therefore anaesthesia. The provision of safe anaesthesia faces challenges arising from physiological adaptations to space, difficulty achieving and maintaining personnel expertise, possible pharmacological changes in anaesthetic agents used, limited consumable shelf-life and provision of intravenous fluids and blood products. In this review article we discuss these challenges in the context of a hypothetical case.

INTRODUCTION

Since the middle of the 20th century, nations have been sending astronauts into space as the new frontier for exploration. The turn of the century has seen a groundswell of interest from national and private bodies in sending a crewed Exploration Class Mission to Mars. NASA has stated plans to send a crew of "at least 4" on a mission of "at least

900 days" to Mars, and private companies such as the MarsOne Project and SpaceX have expressed similar goals(1, 2). A mission to Mars presents challenges that have never been faced, including the management of a medical or surgical emergency on board. Models used to calculate the likelihood of such an emergency suggest that there is likely to be at least one on a 900 day flight(3-5). A medical emergency on board carries a significant risk of morbidity or mortality, as well as risk to the mission itself.

Broadly, the challenge of managing a medical emergency in space is three-fold. Firstly, resources are likely to be limited. Weight restrictions on payload would likely mean that some simple medical consumables (e.g. crystalloid fluids) would be impractical. Radiological and pathological diagnostic support is also unavailable, except for ultrasound(6-8). Secondly, there is likely to be a lack of skilled personnel on board. It has been suggested that the most appropriate Medical Officer would be an emergency physician with broad surgical skills and wilderness medicine training(9, 10), but it is possible that the Crew Medical Officer (CMO) would be a specialist in another field with only basic medical training. Finally, timely evacuation to a terrestrial medical centre is impossible. Evacuation from Mars to Earth would take 9-12 months, and depending on the relative locations of the planets, communication between Earth and Mars could take as long as 20 minutes in each direction(3), making telemedicine impractical. These challenges mean that the emergency will have to be dealt with in its entirety by the crew, using only the resources on board the vehicle.

A HYPOTHETICAL CASE

To illustrate the challenges posed by an emergency, we will discuss the hypothetical case of Dr FH, 35 year old male, PhD (Astrophysics). On day 700 of a 900 day mission to Mars, Dr FH develops acute central abdominal pain which migrates to the right iliac fossa, fever, anorexia and vomiting. Having undergone extensive medical screening as part of his selection and training as an astronaut, Dr FH is otherwise healthy, with no significant medical or surgical history. His appendix is still in situ.

Dr FH has a low risk for less common causes of this presentation, such as caecal diverticulitis or inflammatory bowel disease, but the diagnosis is not simple. The lack of diagnostic imaging or pathology services means that the diagnosis must be purely clinical (with the possible assistance of ultrasound), and possibly made by a non-physician, depending on the composition of the crew.

The CMO decides that, clinically, Dr FH has acute appendicitis. We acknowledge that the benefits and risks prophylactic appendectomy is currently being debated(11, 12), but this topic will not be discussed here. Appendicitis occurs in healthy adults, with a lifetime risk of 8.6 percent in males, and 6.9 percent in females(13). The current standard of practice for acute appendicitis is laparoscopic appendectomy(14).

In this case, non-operative management with empiric antibiotics and intravenous fluid replacement might be a preferred strategy to avoid surgery in space. However, this approach carries the risk of clinical deterioration requiring rescue appendectomy, as well as perforation, abscess formation and peritonitis(11-14). The challenges of providing the intravenous fluids (crystalloid or blood products) required for intravenous antibiotics to be administered in space will be discussed later. Despite the attendant risks, non-operative management may be an option as it may delay the need for appendectomy until the crew has returned to Earth.

Concerned about the risk of failure of conservative management and difficulty in managing a deteriorating clinical situation with 200 days remaining on the mission, the CMO and Dr FH elect to perform an appendectomy. For this paper, we will assume that the CMO has appropriate equipment, training and clinical aids to perform the surgical procedure.

EXISTING LITERATURE

There is a growing body of literature describing surgical techniques that could be used in microgravity, including laparotomy and laparoscopy(15-17). The need for surgery implies the need for anaesthesia, but there is comparatively little evidence on the use of anaesthesia in a weightless environment.

Anaesthesia in microgravity analogues

To date, research on anaesthesia of humans has been limited to space analogues. The disadvantage of this approach is that there is not perfect way to simulate microgravity on earth. Modern analogues simulate only a single aspect of the environment, such as microgravity (parabolic flight, neutral buoyancy studies), physiological adaptations (head down bed rest), or resource limitations. Some minor procedures which would be required for anaesthetic delivery in space have been demonstrated, such as venepuncture of the antecubital fossa(18) and visualisation of thoracic, cardiac, vascular, ocular and joint structures with ultrasound(6-8).

A few studies have demonstrated airway management in microgravity analogues. Endotracheal intubation has been demonstrated in neutral buoyancy (19) and parabolic flight (20) using simulation models. These studies demonstrated the difficulty of intubation of an unrestrained patient, and the difficulty of the skill when performed by novice practitioners. Laryngeal Mask Airway (LMA) insertion in parabolic flight has also been demonstrated.

Pharmacokinetic changes in space and microgravity analogues

A review article by Kast et al. (21) details the limited body of research into pharmacokinetic changes caused by adaptation to microgravity. The two pharmacokinetic studies conducted on subjects in space (22, 23) were limited by sample size and did not show a consistent effect. Four studies examining the pharmacokinetic changes following intravenous administration have been conducted, but these data are difficult to interpret owing to small sample sizes, inconsistent techniques of simulating microgravity (supine position vs 6° head down bed rest [HDBR]) and poor precision of measurements. Seubert et al. (24) studied pharmacokinetic changes of propofol in patients following 48 hours of HDBR, and showed a small decrease in clearance, which may be clinically insignificant, however it is unclear how well HDBR simulates the effect of microgravity on pharmacokinetics, and this study was limited by its small sample size and lack of surgical stimulus. Further research is required before definite conclusions can be made regarding pharmacokinetic changes in anaesthetic drugs.

APPROACH TO ANAESTHESIA

It should be noted that there are two broad approaches to anaesthesia which are being considered for use in an exploration class mission to mars. These are general anaesthesia and regional anaesthesia. In the case of Dr FH, general anaesthesia will be most likely required for intra-abdominal surgery, and this would also be true for surgical approaches to other conditions where regional anaesthesia is not feasible. In general, however, regional anaesthesia is likely to be the preferred option when available. The "Local and Vocal" approach maintains the homeostatic and protective reflexes, reducing the risk of aspiration or cardiovascular complications which may be associated with general anaesthesia. It will also allow the crew member to remain awake during the procedure, and recover quickly afterwards. However, whichever anaesthetic approach is used, it is likely to be complicated by physiological and pharmacological changes due to microgravity.

PHYSIOLOGICAL CHANGES IN MICROGRAVITY

The effect of microgravity on human physiology has implications for the conduct of surgery and anaesthesia in space. Among all the adaptations, there are four that are directly relevant to anaesthesia: reduction in blood volume, changes in cardiac systolic and diastolic function, musculoskeletal wasting and changes in the neuromuscular junction, and slowed gastrointestinal motility and gastric emptying.

Cardiovascular changes

When standing at sea level, circulating blood is pulled towards the legs, resulting in a mean-arterial-pressure gradient across the body. In a microgravity environment, the gravitational force creating this gradient is not present, and thus pressures equalise throughout the body(3, 25-27). This results in redistribution of blood volume from the legs to the torso and head. The apparent increased circulatory volume results in diuresis and contraction of blood volume by around 10-15% within the first week in space(3, 25-27). This is accompanied by cardiac atrophy and a reduction in cardiac output of 17-20%. Komorowski et al. (3) describe the cardiovascular adaptations in detail. The combination of these

factors is likely to result in increased risk of arrhythmia and reduced capacity to compensate for haemorrhage or reduction in peripheral resistance(3, 9, 28, 29). The movement of blood volume in a cephalad direction also produces facial oedema, which could potentially complicate tracheal intubation by worsening the grade of view.

Musculoskeletal changes

The loss of bone and muscle mass in microgravity environments has been well documented(30) and known since the early days of space flight. Modern astronauts can maintain bone density through exercise but may still be prone to fracture due to poor bone quality. Exercise programs in space have helped astronauts in maintaining muscular endurance, but skeletal and cardiac muscle atrophy in space remains a problem(3). Disease models in humans that also display skeletal muscle atrophy (e.g. Guillain Barré (29)), and microgravity analogue studies in animals(31, 32) suggest that acetylcholine receptor changes may accompany skeletal muscle atrophy. This implies a risk of hyperkalaemia following administration of Suxamethonium to astronauts in space(3, 28, 29), and excludes Suxamethonium as an agent for use in rapid sequence induction. In addition to muscle atrophy, changed in fat deposition may impact the pharmacokinetics of anaesthetic drugs by affecting the volume of distribution.

Gastrointestinal changes

It has been suggested that gastric emptying is slowed in the first 72 hours of space flight, possibly due to space motion sickness(3, 5, 33). Two spaceflight studies have shown variable absorption of paracetamol, used as a marker of gastric emptying(21-23). This has implications for in-flight anaesthesia, as any delay in gastric emptying increases the risk of regurgitation and aspiration following induction of anaesthesia, as well as a delay in absorption of any orally administered medications.

ANESTHETIC CONSIDERATIONS

Personnel Expertise

The exact composition of the crew for a mission to Mars is unknown, but a diverse range of skills and specialties are required to operate the various systems. There is a history of physicians in the crew of the International Space Station (ISS) (34). However, there is no requirement that the CMO is a physician. In the case that the CMO is a physician, it is also possible that they do not have expertise in the anaesthetic skill set unless their background is in emergency medicine or anaesthetics. Anaesthesia in austere and resource poor environments (such as low-to-middle income countries) or in isolated or confined environments, suggest that anaesthesia can be provided by non-medically trained personnel(35). However, the capacity to deal with complex cases will be limited. Komorowski et al. suggest that the ideal practitioner would be an emergency physician with surgical and wilderness medicine training(35).

Intravenous cannulation with the administration of fluids has been demonstrated in weightlessness by non-physicians in parabolic flight simulations(18). Venepuncture of the anterior cubital fossa performed by astronauts on the ISS suggests that intravenous access would not be expected to be difficult. Intraosseous access devices could also be utilised, and a few studies suggest that induction of anaesthesia by this method is possible(36).

Intubating laryngeal mask airway (ILMA) insertion has also been demonstrated in weightlessness by non-physicians in parabolic flight simulations. Endotracheal tube insertion (ETI) by anaesthetists in a neutral buoyancy environment has been shown to be difficult without restraint(19), and a study of ETI in parabolic flight by novice operators showed an unsatisfactory rate of correct placement and ventilation(20), but this result is difficult to interpret due to the extreme time restriction in parabolic flight. Laryngeal mask insertion has many favourable properties over ETI, which include ease and speed of use, elimination of the risk of oesophageal intubation, and lack of requirement for muscle relaxing agents(9). The risk of pulmonary aspiration of regurgitated gastric contents with an LMA in situ appears to be no higher than ETT. However this has only been observed in 1G, by trained anaesthetists with well fitting devices in well selected patients (37). Astronauts may be at increased risk of aspiration due to the possibility of delayed gastric emptying and increased gastrointestinal transit time(3, 5, 33). In this case, ETI may be a preferred method of airway management, despite the other

disadvantages. A recent study of rapid sequence induction including ETI in a Mars analogue environment demonstrated satisfactory ETI by non-physicians(38), but whether this skill can be satisfactorily transferred to a weightless environment remains to be demonstrated. The Clinical Outcome Metrics for Optimization of Robust Training (COMFORT) study commissioned by the National Space Biomedical Research Institute has also demonstrated that numerous medical procedures, including ETI, can be performed safely by non-physicians even up to 9 months after initial training when provided Just-In-Time training (39).

The possibility of conducting regional anaesthesia in space has been discussed(3, 28, 40), and has significant benefits compared with general anaesthesia. These include the patient being conscious throughout the procedure (thus retaining access to their critical skillset), eliminating the need for muscle relaxation or airway management, rapid recovery, and good post-operative pain relief. It has been suggested that as few as three regional nerve block techniques would enable a wide array of limb surgery: Axillary, brachial, femoral, and subgluteal sciatic blocks(9). Identification of anatomical structures by ultrasound has been performed by astronauts on the ISS using the on-board ultrasound machine(6-8). It is therefore plausible that regional anaesthesia could be performed in space. However, this implies a significant training requirement for the crew. Depending on the technique in question, the number of procedures required to achieve an acceptable success rate can be a few as 20 (for femoral nerve blocks) or as many as 62 (in the case of axillary brachial blocks)(28). Once a crew member has been deemed competent, then skill maintenance becomes the challenge. However, just-in-time training may have a role in refreshing the required skill immediately before its performance(8, 39). Furthermore, all blocks carry a risk of failure, and failure of a block implies the need to perform the procedure under general anaesthetic.

Pharmacological Considerations

Physiological changes with microgravity may have an impact on the pharmacokinetics and pharmacodynamics of anaesthetic agents. Two pharmacokinetic studies have been performed in humans in space(22, 23), and there is a small body of literature investigating pharmacokinetic parameters of different medications in microgravity analogues(21, 24, 29, 33, 41-43). It is worth noting that volatile anaesthetic agents are not suitable agents for maintenance of general

anaesthesia in space. The use of volatile anaesthetics in the closed environment would potentially expose the rest of the crew, and current vaporiser technology relies on gravity to separate the gas phase from the oily phase, and as such would not function in space(28, 40). Thus, total intravenous anaesthesia is required.

Propofol is a very commonly used agent for induction and maintenance by Total Intravenous Anaesthesia (TIVA). It has the advantages of a rapid onset of action and is safe. Its undesirable effects include a reduction in total peripheral resistance and negative cardiac inotropy. The cardiovascular changes in microgravity of contraction of circulating volume, cardiac atrophy and reduction in cardiac output might predispose astronauts to hypotension following induction, requiring pressor therapy(28). One study of Propofol in subjects following 48h of head-down bed rest suggests that anaesthetic doses of Propofol in 1G and microgravity might be similar(24). However, the study was limited to anaesthesia only without a surgical stimulus, and the results have not been replicated in space.

Furthermore, Propofol has an approximate volume of distribution of 70L and may be less impacted by contraction of circulating volume than anaesthetic agents with a lower volume of distribution, such as Ketamine, however reduction of total body volume by wasting of skeletal muscle may reduce the dose of Propofol required. It should also be noted that many conventional syringe drivers use a proprietary algorithm to maintain anaesthesia with TIVA by Propofol, and the algorithm uses a model which assumes a body composition and volume of distribution in 1G. These models may not be valid in the context of the physiological adaptations in microgravity.

Ketamine is another anaesthetic agent which can be used for induction and maintenance of general anaesthesia. It has been suggested as an alternative anaesthetic agent for use in space due to some potential advantages, which include(28, 29).

- Favourable cardiovascular profile in patients with hypovolaemia
- High therapeutic index compared to propofol
- Rapid onset of action
- Long shelf life in crystal form
- Preservation of airway reflexes, maintenance of spontaneous ventilation, reduction in oxygen requirement

- Multiple potential routes of administration

Ketamine thus has numerous favourable properties in the hands of a non-physician anaesthetist in space. It carries much less risk of cardiovascular collapse, it minimises the requirement for definitive airway management (although the risk of vomiting requires access to an oropharyngeal suction device), the risk of lethal overdose is low, and its long shelf life means it is likely to remain in-date for the duration of the mission. This needs to be demonstrated in pharmacodynamics studies. The potential undesirable effects of Ketamine include emergence delirium, higher risk of post-operative nausea and vomiting and awareness, and its use in head injuries is controversial. While Ketamine is likely to have favourable pharmacodynamic properties in the context of physiological changes in microgravity, the pharmacokinetic changes are unknown. There is speculation that, due to its low volume of distribution of 3L, the pharmacokinetic profile of Ketamine may be more significantly impacted by the circulating volume contraction than Propofol. Further research is required if Ketamine is to be used as an anaesthetic agent in space.

At least in the case of Dr FH, an open appendectomy implies the requirement for muscle relaxation. It has been proposed that skeletal muscle atrophy in space could complicate the choice of paralytic agent(31, 32, 44-47). Skeletal muscle atrophy in disease analogues (such as Guillain Barré Syndrome) is accompanied by changes in neuromuscular junction nicotinic acetylcholine receptors(29). Use of a depolarising neuromuscular junction blocking agent (i.e. Suxamethonium) in this context is associated with a risk of hyperkalaemia and fatal cardiac arrhythmia(29). It is unknown whether this is also the case in astronauts. However, it seems prudent to exclude the use of Suxamethonium on this basis. Rocuronium may be the preferred neuromuscular junction blocking agent in space, due to its rapid onset of action at high doses(28) and the availability of a reversal agent, Sugammadex.

Logistical Considerations

Medication Shelf-Life

The planning parameters set by NASA in 2015 are that a mission to Mars would comprise a crew of "at least 4" and take "up to 1100 days"(1, 2). A

mission of this duration implies significant logistical challenges for the medical consumables required for the provision of anaesthesia. An 1100 day mission would require medications with a shelf-life exceeding that duration.

In Australia, the shelf-life stated by manufacturers is limited by regulation to 3 years. This does not always reflect actual stability however, for example Ketamine can be formulated as an anhydrous crystal and has a shelf-life of about 20 years(28), ideal for use in exploration class space missions. The manufacturers of Esmeron® (Rocuronium), Bridion® (Sugammadex) and Diprivan® (Propofol) were contacted for extended stability data beyond the stated year shelf life(48-50). The manufacturer of Bridion® provided data on file for Bridion®, which confirmed the three year shelf-life(51). No extended stability data was made available for Esmeron(51). The manufacturer of Diprivan declined to provide extended stability data on the basis of confidentiality(52). A mission of 1100 days (which is within the timeframe NASA is planning for a mission to Mars(1, 2)) would exceed the shelf-life of each of the above formulations of Propofol, Rocuronium and Sugammadex.

Furthermore, the environment of space appears to be more hostile to pharmaceuticals than Earth. Stability studies of medications returned from the ISS suggest that this shelf-life may be reduced (53, 54). Some medications returned for resupply from the ISS had degraded more than 10% of the active ingredient before the expiry date. The authors postulate that the high exposure to radiation in space may contribute to this enhanced degradation rate (53). This has significant implications for the viability of any medication on a long duration mission to Mars, and there is currently no available data on any of the anaesthetic medications being considered, which include local anaesthetics for regional anaesthesia. There is the potential that exposure to radiation may produce unusual degradation products which may be harmful on administration, rather than just ineffective, although no such products were identified in the studies. Further research is required to develop formulations with improved stability if these drugs are to be used to deliver anaesthesia in space.

Intravenous Fluids and Blood Products

Crystalloid intravenous fluids (e.g. normal saline, compound sodium lactate) are routinely used during surgery as maintenance fluid to prevent dehydration following fasting; for fluid resuscitation in hypovolaemia; and as a medium for delivery of

intravenous infusion of drugs. Provision of crystalloid fluids in space is likely to be very expensive; in 2008, NASA estimated the cost of launching one pound of payload into orbit at USD\$10,000(55), although the advent of private space transportation companies is likely to have reduced this figure through competition, and innovations like high-payload re-usable launch vehicles such as the SpaceX Falcon Heavy (56-58). Each litre of crystalloid fluid weighs approximately 1kg or 2.2lb, thus “due to mass and volume limitations, space vehicles cannot carry sufficient IV fluid for medical contingencies”(59). NASA has developed a prototype IV fluids generation system for production of intravenous fluids in space, which generates purified water to be added to bags with pre-measured solutes to produce Normal Saline(59). Further research is required to determine if the product is suitable for medical use.

In cases of hypovolaemia due to haemorrhage, blood products are the preferred means of volume resuscitation, however, due to mass, volume and shelf life, it is not feasible to include pre-prepared blood products in the payload. If blood products are to be administered, they will need to be donated by the other members of the crew. The concept of a “walking blood bank” has been practiced in combat zones by military organisations (60), and the stringent medical standards required of astronauts suggest that they may be a suitable population for this technique. For example, it is possible (though perhaps unlikely) that the entire crew are of the same, or compatible, blood types, able to donate to, and receive from, any other crew member. This has the advantage of a large potential donation pool if a massive transfusion is required, but has the possible disadvantage of limiting the potential pool of crew members. Alternatively, the crew could be allocated into compatible donor/recipient pairs, which would minimise the restriction on crew selection, but may reduce the amount of blood product available to the recipient.

POSSIBLE ANAESTHESIA REGIMEN

Before proposing a single anaesthetic regimen, it is worth highlighting that the anaesthetic regimen used will depend on the skill of the medical officer. If an emergency physician with specialist training is part of the crew, then they would be in the best position to decide on how to proceed. A single regimen will not be ideal in all situations. However,

it may be necessary to specify a general regimen as a fall back if the physician is the patient.

A single general anaesthetic regimen would simplify anaesthesia training and reduce cognitive burden on the crew performing the procedure before surgery. Dosages of medications should be calculated in advance for each crew member to minimise the risk of dose calculation, but it should be recognised that this is potentially fraught due to the unknown effect of physiological adaptations on pharmacology and pharmacokinetics.

To return to the case, Dr FH requires intra-abdominal surgery, which necessitates general anaesthesia with muscle relaxation. Dr FH's weight before launch was 70kg, and pre-calculated doses will be used. His current mass is unknown, and difficult to measure in the weightless environment! A possible anaesthesia regimen is proposed below:

0 min: Gain IV/IO access. Premedication avoided as increases aspiration risk in RSI particularly if vomiting risk is high.—Preoxygenation with 100% O₂ via mask. Attach monitoring equipment (non-invasive BP, ECG, pulse oximetry). Implement the restraint system in preparation for surgery.

5 min: Induction of anaesthesia with Ketamine 150mg IV by slow push (2mg/kg) over 60 sec. Assess ease of ventilation by bag/mask.

6 min: Muscle relaxation by Rocuronium 1.2mg/kg.

7 min: Intubation with an endotracheal tube (a half size smaller than would be required on earth, to account for oedema) by video laryngoscopy. Commence Ketamine maintenance infusion at 10–45 micrograms/kg/minute, depending on response, using IV fluids generated on board.

8 min: Commence surgery. Further doses of Rocuronium after 40-50 mins as required.

Conclusion of surgery: Reversal of Rocuronium with Sugammadex 650mg IV (8mg/kg). Discontinue Ketamine infusion. Provide an initial dose of post-operative analgesia with Fentanyl, monitor Dr FH and extubate when appropriate. Further post-op pain relief could be given orally.

CONCLUSION

The capability to provide anaesthesia on an exploration mission to Mars will be essential to the successful completion of the mission.

Physiological adaptations to microgravity may complicate any provision of anaesthesia. There are many challenges to this capability, arising from difficulties in providing and maintaining the required anaesthetic skill set (including airway management and regional anaesthesia), the logistical problem of providing enough consumables that will remain viable for the duration of the mission, and a lack of knowledge regarding any pharmacokinetic or pharmacodynamic changes in drugs administered in microgravity.

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