Safe duration of postoperative monitoring for malignant hyperthermia patients administered non-triggering anaesthesia: an update

C. Barnes*, K. M. Stowell†, T. Bulger‡, E. Langton§, N. Pollock**

Summary

The postoperative care of malignant hyperthermia (MH) patients is subject to international variation, with a paucity of data in the literature to guide management. Over a series of three studies, our aim was to evaluate whether MH-susceptible patients (and relatives who had not yet been investigated), who had received a non-triggering anaesthetic, could be managed in the same way as the standard surgical population. Following a retrospective study, 206 anaesthetics were administered in a prospective second study to MH-susceptible/related individuals who were monitored for a minimum of one hour in the post anaesthesia care unit and a further 90 minutes in a step-down facility. No problems relating to MH were encountered. The postoperative monitoring time was subsequently changed and, in a third study, patients were managed no differently from standard surgical patients. One hundred and twenty-five anaesthetics were administered with no evidence of problems. This data shows that standard postoperative monitoring times are safe and appropriate in MH-susceptible patients.

Key Words: malignant hyperthermia, PACU, non-triggering anaesthetic, MH clinical grading scale, stress, ryanodine receptor, temperature monitoring

The purpose of this study was to evaluate whether malignant hyperthermia (MH) patients can be safely monitored in the post anaesthetic care unit (PACU) for the same duration as standard non-MH patients, when exposed to non-triggering anaesthesia. This study updates data previously published from our institution[1]. How long these patients should be monitored is not well studied[1,2] and international practices of postoperative monitoring are variable, ranging from conservative to treating these patients no differently from standard patients[1,3–6]. Wappler stated that "for how long patients should be monitored postoperatively is not well studied"[6]. The traditional postoperative monitoring of MH-susceptible (MHS) patients who had undergone a trigger-free anaesthetic was four hours in PACU[7]. This can be difficult with young children and increases costs[1]. There is no data published in the literature to support the safety of standard monitoring, so this unit has conducted a series of three studies to establish the safety of reducing the postoperative monitoring period.

* MBChB, FANZCA, Specialist Anaesthetist, Department of Anaesthesia, Hutt Hospital, Lower Hutt, New Zealand
† BSc(Hons), PhD, Associate Professor and Senior Lecturer in Biochemistry, Institute of Fundamental Sciences, Massey University, Palmerston North, New Zealand
‡ MBChB, FANZCA, Specialist Anaesthetist, Department of Anaesthesia and Intensive Care, Palmerston North Hospital, Palmerston North, New Zealand
§ MBChB, FANZCA, Specialist Anaesthetist, Department of Anaesthesia and Pain Medicine, Wellington Regional Hospital, Wellington, New Zealand
** MBChB, FCA, FANZCA, MD, Anaesthetist, Department of Anaesthesia and Intensive Care, Palmerston North Hospital, Palmerston North, New Zealand
Address for correspondence: Dr Neil Pollock. Email: neilp@midcentraldhb.govt.nz
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The first study retrospectively established that there were no problems relating to MH in 254 anaesthetics where the patients had been monitored in PACU for four hours[1]. Based on these findings, a second, prospective study from 2000 to 2008 demonstrated that one hour of monitoring in PACU followed by 90 minutes in a step-down unit was safe[1]. Again, there was no evidence of MH in this group of patients. Complete data from this second study are included in this publication.

In view of the normal findings in the second study, our study involved documentation of standard monitoring in PACU in a large group of MHS patients or relatives and standard monitoring in the step-down unit. This third study extended from November 2008 to September 2013 and results are reported below.

Methods

Our institution serves a relatively large MHS population, as well as many potentially susceptible genetic/blood relatives (about 1 in 150 patients presenting for anaesthesia are MHS or related to MHS families [unpublished data, Mid-central District Health Board, Department of Anaesthesia]). A database of MHS patients has been maintained since 1991 and includes all known susceptible individuals or potentially susceptible relatives. MHS patients presenting for surgery are identified by history, reviewing previous hospital records, contacting relatives and checking the locally-held database. For the extension of the second study, PACU and step-down unit data were entered into an already established dedicated database[1] and, for this third study, a further additional dedicated database was established.

All MH testing in New Zealand was undertaken in Palmerston North; in vitro contracture testing (IVCT) was performed at Palmerston North Hospital and DNA analysis at Massey University. The European Malignant Hyperthermia Group protocol is followed for IVCT[8]. Patients are categorised as 'MHS' or 'MHN' (MH normal)—categories that were established at the 32nd European Malignant Hyperthermia Group Annual Scientific Meeting[4]. Patients who have relatives susceptible to MH but have not been tested are designated 'no biopsy done' (NBD). In general, these patients are too young for testing or have declined testing for a variety of reasons. DNA-positive patients who do not require a biopsy are included in the MHS group.

Methods of the first study have been published previously[1]. Methods and some early results for the second study have also been previously published[1] and these early results are included. In brief, on transfer to the PACU, a set of recordings were immediately taken: pulse rate (PR), respiratory rate (RR), temperature, blood pressure, end-tidal carbon dioxide ($ETCO_2$) (adult capnography mask, Fairmont Medical, Bayswater, Victoria, and nasal sampling line, GE Healthcare, Auckland, New Zealand) and oxygen saturation of haemoglobin. These were taken every 15 minutes for one hour and, if stable, the patient was discharged to a step-down unit, a holding area for day cases where a further set of three recordings were taken at 30-minute intervals (omitting $ETCO_2$). The patient could be discharged at the end of this period or earlier if stable. Alternatively, the patient was discharged to the ward at the end of an hour and standard ward recordings taken—hourly for four hours and then four-hourly. MH patients in the ward were managed in the same way as non-MH patients.

For this third study, upon admission to the PACU, a set of recordings were taken as above. These were taken every 15 minutes for 30 to 45 minutes until the patient was ready for discharge. An initial temperature was taken and this may or may not have been repeated, depending on the initial result. From PACU, the patients were discharged to the step-down unit or the ward. In the step-down unit, one set of recordings was taken within 30 minutes of admission. These may or may not have been repeated depending on the initial result. The aim was to discharge the patient within one hour. Ward patients were managed as above, the same way as standard (non-MH) surgical patients.

Further assessment was indicated if the temperature was recorded >38.8°C or if a tachycardia was sustained for no obvious reason (>120/minute for more than 20 minutes). Creatine kinase measurement was undertaken occasionally.

For day cases, patients and caregivers were given verbal and written advice to contact the hospital duty anaesthetist if any problems developed (muscle aches/stiffness, high temperature, dark urine) and the patient or caregivers were each followed up the next day with a phone call from a PACU nurse. Any actual problems were recorded in the database.

All patients were given non-triggering anaesthesia, i.e. propofol infusion with opioids and a non-depolarising muscle relaxant if indicated. A dedicated vapour-free anaesthetic machine was used for all general anaesthetic cases.

Results

For the purposes of this study, patients 16 years of age and under are called children and those 17 years and over are adults.

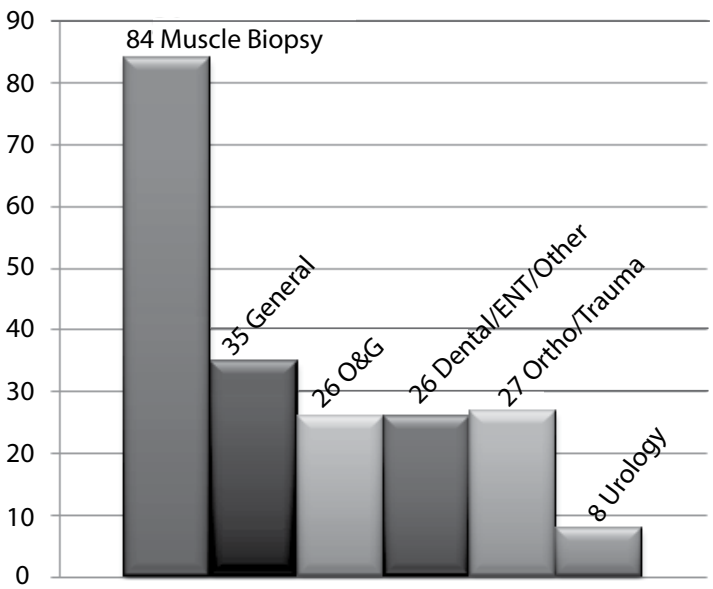

Figure 1: Range of surgical procedures in Study 2. O&G=obstetrics and gynaecology, ENT=ear, nose and throat.

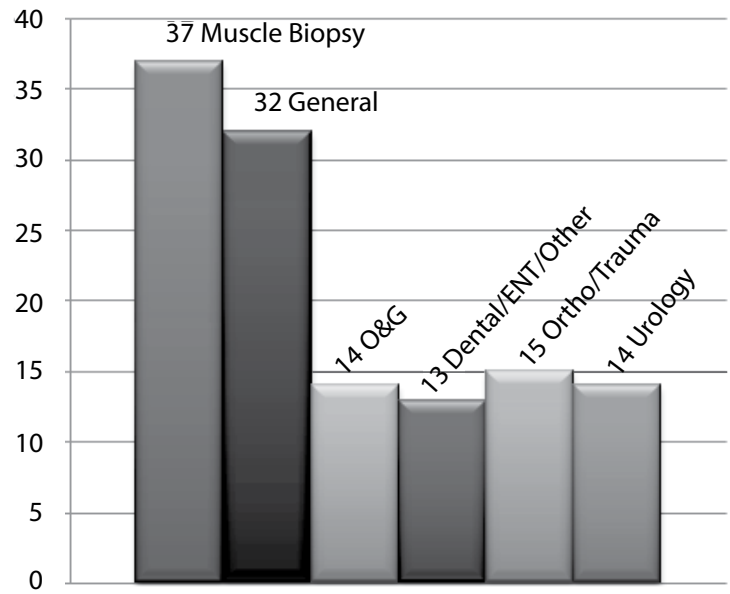

Figure 2: Range of surgical procedures in Study 3. O&G=obstetrics and gynaecology, ENT=ear, nose and throat.

Study 1

The first study has been published previously and included 254 anaesthetics, where patients were monitored in PACU for four hours. There were no episodes of MH[1].

Study 2

From November 2000 until October 2008, there were 206 anaesthetics involving 190 MHS or NBD patients. Of these, 129 were performed on MHS patients and 77 on the NBD patients. Ages ranged from one to 73 years (mean 35 years); the NBD group had a mean age of 18 years and the MHS group 37 years. Anaesthesia time varied from 2 minutes to 4 hours 20 minutes (mean 67 minutes). There were 177 general anaesthetics (85.9%), 28 regional anaesthetics (13.6%) and one patient had a combined technique (0.5%). Surgical procedures are shown in Figure 1. Using the MH clinical grading scale (MHCGS), there were no perioperative MH reactions[10].

The PACU data and post PACU data of Study 2 is shown in Tables 1 and 2, respectively. The maximum value for each parameter was recorded, except for saturations where the lowest value was entered. There were abnormal findings, e.g. tachycardia, but this was not accompanied by other signs of MH. Children, in general, had higher PRs and RRs, but these were also isolated findings. There were several raised $ETCO_2$ measurements, indicating hypoventilation, and low saturations were briefly recorded in several individuals but there were no other signs of MH. No patient developed a temperature >38°C in the PACU. One patient had a change in temperature of 1.9°C (35.7°C to 37.6°C); this was a child for a day-stay tonsillectomy who was subsequently admitted to the ward for observation. The child received paracetamol, the temperature subsequently settled down without further investigation and she was discharged the following day.

The average time spent in the PACU in this group was 76 minutes although, only forty-one patients (19.9%) stayed longer than one hour. Most reasons for delay were patient transfer problems but discharge was delayed in others due to pain or excessive sedation (two patients for each), confusion, hypotension, hypothermia, the requirement for prolonged recovery due to a prolonged surgical procedure, drug reaction to metoclopramide and the need for non-invasive respiratory support. Nausea (one patient), pain (two patients), tachycardia (five patients), minor pyrexia (six patients), oxygen saturation of haemoglobin <95% (one patient) and bleeding (one patient) were the only problems noted in the step-down unit. Overall, in this study, most patients ranked 1 or 2 on the MHCGS and no patient ranked higher than a 3 (a 'somewhat less than likely' likelihood of a reaction). Five patients had a normal serum creatine kinase measurement and there was no indication for arterial blood gas measurements.

Patients were monitored for up to 90 minutes in the step-down unit and the range of recordings from this unit or the ward are shown in Table 2. There were no significant problems and those with shorter procedures were discharged earlier within this time period. Seventy-one percent of procedures were managed as day stay.

Study 3

Between November 2008 and September 2013, 125 anaesthetics were administered to 60 MHS and 55 NBD patients (67 and 58 anaesthetics respectively, as some patients were anaesthetised on multiple occasions). Over the two groups, ages ranged from 15 months to 78 years (mean 33 years); the NBD had a mean age of 21 and the MHS group 33. Anaesthesia time varied from 15 minutes to 4 hours 55 minutes. All patients received general anaesthesia. Surgical procedures are shown in Figure 2. Muscle biopsies accounted for 37 (31%) of the procedures.

The PACU data for Study 3 is shown in Table 3. As expected, children tended to have higher PRs and RRs. One patient developed a temperature of 38.4°C in PACU. This was a woman who had an emergency caesarean delivery under general anaesthesia. She was started on antibiotics for a postoperative rise in temperature that settled down promptly and was not further investigated. No patient ranked higher than 3 (a 'somewhat less than likely' likelihood of a reaction) on the MHCGS[10]. The majority ranked 1 or 2. The average time spent in the PACU in this group was 49 minutes. Transfer problems and pain control were the main reasons for delays in discharge.

Table 1

Study 2: PACU recordings

Recording	MHS, n=129 range (mean)	NBD, n=77 range (mean)
PR (/min)	35–114 (63)	45–125 (80)
Systolic BP (mmHg)	58–170 (109)	75–165 (123)
Temperature (°C)	34.8–37.6 (36.1)	34.7–37.9 (36.5)
$ETCO_2$ (mmHg)	16–62 (38)	10–64 (40)
SpO_2 (%)	89–100 (98)	88–100 (98)
RR (/min)	8–30 (16)	10–32 (18)

PACU=post anaesthesia care unit, MHS=malignant hyperthermia susceptible, NBD=no biopsy done, PR=pulse rate, BP=blood pressure, $ETCO_2$=end-tidal carbon dioxide, SpO_2=oxygen saturation of haemoglobin, RR=respiratory rate.

Table 2

Study 2: post-PACU recordings (on ward or DOSA)

Recording	MHS, n=129 range (mean)	NBD, n=77 range (mean)
PR (/min)	44–95 (67)	57–119 (83)
Systolic BP (mmHg)	82–165 (120)	89–150 (117)
Temperature (°C)	34.7–37.5 (36.2)	35.4–38.0 (36.6)
SpO_2 (%)	95–100 (98)	94–100 (98)
RR (/min)	10–22 (15)	12–26 (18)

PACU=post anaesthesia care unit, DOSA=day-of-surgery admission, MHS=malignant hyperthermia susceptible, NBD=no biopsy done, PR=pulse rate, BP=blood pressure, SpO_2=oxygen saturation of haemoglobin, RR=respiratory rate.

Table 3
Study 3: recordings in PACU

Recording	MHS, n=65 range (mean)	NBD, n=60 range (mean)
PR (/min)	40–100 (75)	55–158 (91)
Systolic BP (mmHg)	75–150 (124)	105–172 (136)
Temperature (°C)	34.5–37.8 (36.1)	35.5–38.4 (36.4)
$ETCO_2$ (mmHg)	29–49 (39)	37–54 (43.5)
SpO_2 (%)	95–100 (98)	95–100 (97)
RR (/min)	10–20 (12)	12–24 (18)

PACU=post anaesthesia care unit, MHS=malignant hyperthermia susceptible, NBD=no biopsy done, PR=pulse rate, BP=blood pressure, $ETCO_2$=end-tidal carbon dioxide, SpO_2=oxygen saturation of haemoglobin, RR=respiratory rate.

Table 4
Study 3: post PACU recordings

Recording	MHS, n=65 range (mean)	NBD, n=60 range (mean)
PR (/min)	45–100 (72)	44–140 (88)
Systolic BP (mmHg)	80–180 (116)	90–190 (128)
Temperature (°C)	35.5–38.4 (36.5)	35.6–37.2 (36.4)
SpO_2 (%)	92–100 (98)	92–100 (97)
RR (/min)	12–20 (15)	12–26 (18)

PACU=post anaesthesia care unit, MHS=malignant hyperthermia susceptible, NBD=no biopsy done, PR=pulse rate, BP=blood pressure, SpO_2=oxygen saturation of haemoglobin, RR=respiratory rate.

The step-down unit/ward data are shown in Table 4. There were a number of isolated tachycardias, particularly in young children. One patient developed a temperature of 38.4°C on discharge to the ward. She had a strong family history of MH and had a positive muscle biopsy and DNA test. She had had a three and a half-hour bowel resection procedure and had been observed in PACU for two hours. The temperature was isolated with no other evidence of MH. She was reviewed on two occasions and her temperature gradually settled over two to three hours without further treatment. Several other patients had low saturations of uncertain cause but with no other evidence of MH and one patient complained of an itch. No other significant problems were encountered. Fifty-two percent of cases in this group were discharged the same day.

Intraoperative parameters were recorded for each study and were identical to the PACU parameters. Using the MHCGS, the majority of patients ranked 1 or 2, indicating an 'unlikely' likelihood of an MH reaction. Temperature intraoperatively was measured, though not consistently, and 67 out of 125 measurements were recorded ranging from 35.0°C to 37.5°C.

Discussion

Previously, it was suggested that MHS patients should be monitored for at least four hours in PACU and receive a further 24 hours of inpatient monitoring, even after minor surgery[7,11] but increasingly it is recognised that, with appropriate planning, MHS patients can have anaesthesia in ambulatory surgery centres[12]. Same-day discharge after uncomplicated ambulatory surgery is now considered safe[1,11,13]. Improved anaesthetic and surgical techniques[14] have contributed to this policy, improving the cost-effectiveness of day-case surgery and limiting escalating healthcare costs.

MH reactions in the postoperative period have been well described[15–19]. A review of the suspected cases of postoperative MH in the North American Malignant Hyperthermia Registry from 1987 to 2005 found that, of 528 possible cases, only ten were considered 'likely' MH reactions[18]. All of these patients received triggering agents and all showed signs of MH within 40 minutes of cessation of anaesthesia. A further report of postoperative MH had signs within 25 minutes of cessation of anaesthesia. This patient also received a triggering anaesthetic[19].

Reports of non-triggering anaesthetics leading to suspected MH are well documented[20–34] and are, in almost all cases, inconclusive (incomplete biochemical indices and a ranking of 3 or less on the MHCGS)[10]. In a review of potential MH reactions in North America from 1987 to 2006[35], there was one possible MH reaction in a patient who did not receive triggering agents, out of 284 MH events (0.4%). This reaction occurred 15 minutes after the induction of anaesthesia in an otherwise well two-year-old with a positive family history of MH undergoing dental extraction. The anaesthetic machine was appropriately flushed. She was graded as 'almost certain' on the MHCGS[36]. However, there is no documentation of muscle biopsy testing in this child. Another review of reported cases from 1940 to 1992 showed that a significant number out of 503 cases occurred in the absence of known triggering agents. Our critique of this review is that IVCT results are not reported, DNA analysis was not available and coding difficulties make the diagnosis of MH questionable[37]. Notably, this review predates the clinical grading scale to predict MH (MHCGS), which was developed as a standardised means of estimating the qualitative likelihood of MH in a given patient without the use of specialised diagnostic testing[10]. Fifteen of these events occurred in the absence of anaesthesia, though diagnosis of these cases as MH is doubtful.

The proposed possible trigger for MH in patients who are not exposed to a known anaesthetic triggering agent is the stress of anaesthesia and surgery. Susceptible pigs can have MH reactions as a result of exposure to stressful situations, transport, exercise or heat. Similarly, genetically-engineered mice show signs of MH with excessive heat exposure[38,39]. The evidence for stress-induced MH in humans is increasing. Emotional[40,41], heat-related[42,43] and particularly exercise stress have been documented. Tobin reported the most convincing event associated with exercise stress[44], but other reports have been published[45–47].

MH in the majority of cases is associated with mutations in the ryanodine receptor (RyR1) gene. Variants in the RyR1 gene have been associated with MH in 50% to 70% of susceptible families[48]. There are reports of rhabdomyolysis and exertional myalgia associated with positive IVCT[49] and RyR1 gene mutations and dihydropyridine receptor mutations[46,50–53] and hence, the supposed association of MH with stress. Heat-related events corresponding to recent findings in animal models of MH susceptibility and, in one family, intercurrent infection[51], have been associated with RyR1 variants[54].

The RyR1 gene encodes the skeletal muscle calcium-release channel located in the sarcoplasmic reticulum of the muscle cell. It is a large structure and releases calcium stored in the sarcoplasmic reticulum following stimulation of the dihydropyridine receptor. The gene is composed of >15,000 coding-base pairs encoding a receptor of >5000 amino acids. Leakage of calcium from RyR1 has been described in MHS individuals with a mutation and in non-MH individuals[39,55]. It has been suggested that this is a result of increased generation of reactive oxygen species and reactive nitrogen species, particularly the latter. This results in the formation of nitric oxide and hyper S-nitrosylation of the RyR1 protein. S-nitrosylation of the channel results from attachment of nitric oxide to the sulphur atom of cysteine residues in the RyR1 and increases the open probability of the channel allowing increased leakage of calcium. This particularly sensitises the receptor to heat and exercise stress[39,56–60]. These mechanisms have been suggested to explain stress-related episodes.

Apart from the questionable case reports quoted, there is no other evidence that the stress of anaesthesia and surgery alone can trigger an MH reaction. The findings in this paper from 585 anaesthetics suggest that the stress of anaesthesia and surgery does not itself trigger malignant hyperthermia.

Kalow and Britt first described the muscle biopsy test in 1970, modified by Ellis in 1971. A standardised method of testing was published by the European Malignant Hyperthermia Group in 1984[8]. Three categories of diagnosis were recognised: 1) 'susceptible', indicating abnormal contractures to both halothane and caffeine, 2) 'normal' and 3) 'equivocal', indicating an abnormal contracture to either halothane or caffeine, though these patients were regarded as susceptible to MH until proved otherwise. These categories differed from the North American Malignant Hyperthermia Group, where categories of positive and normal tests only are recognised. At the European Malignant Hyperthermia Group's 32nd Annual Scientific Meeting[9], the 'equivocal' category was eliminated and equivocal patients are now regarded as 'MHS(h)' or 'MHS(c)', referring to abnormal contracture to either halothane or caffeine, respectively. In this study, equivocal patients have been included in the MHS group.

MHS patients can be managed with total intravenous anaesthesia. Contraindicated drugs are few and include potent inhalational agents and depolarising muscle relaxants. Caffeine concentrations in beverages are much less than the concentration required to cause contractures in MHS muscle[61]. The preservative 4-chloro-m-cresol is a potent MH trigger but preparations contain concentrations well below that needed to trigger an MH reaction[62]. Other drugs including opioids, nondepolarising muscle relaxants and non-steroidal anti-inflammatory drugs are safe to use. Dantrolene prophylaxis is not indicated.

Intraoperative monitoring is standard, including PR, blood pressure, oxygen saturation of haemoglobin, $ETCO_2$ and, usually, temperature and RR. $ETCO_2$ was often recorded in PACU but this practice has now been discontinued. Sessler recommended temperature monitoring during most general anaesthetics exceeding 30 minutes and all general and regional anaesthetics lasting more than one hour[63]. Laryngeal mask airways can be reused if an idle period of 15 hours is observed following autoclaving[64]. However, most would use new disposable laryngeal mask airways. Flushing the anaesthetic machine is time-consuming[65] and recently activated charcoal filters have been introduced[66]. Activated charcoal filters have been increasingly used in New Zealand and reduce the time for flushing the anaesthetic machine at ten litres per minute to three minutes and replacing the soda lime and circuit. It has been demonstrated that it is safe to recover patients in the same area as patients exhaling triggering agents, as long as PACU ventilation is appropriate[67]. The patient can be discharged in the same way as a surgical patient.

This study has several limitations. In this study, 585 anaesthetics were administered to MHS or related individuals. No MH reactions occurred. Statistically, using 95% confidence intervals, the risk of an MH reaction is 0% to 0.5% although we believe the actual risk is closer to zero. However, only 54.7% were MHS or DNA-positive. The NBD category comprised 45.3% but, as MH has autosomal-dominant inheritance, it could be assumed that about 50% of the latter group would be susceptible to MH. This would reduce the number of MHS anaesthetics to 453 or 77% of the group. Confidence intervals would still limit the risk to 0% to 0.66%. Not all parameters were recorded for all patients. Recording of intraoperative temperature was variable. The patients' temperatures were almost always documented in PACU and in the ward. This is a reflection of what happens in clinical practice.

In summary, this study indicates that MHS and related patients can be managed in the same way as standard patients in PACU, provided they have had a non-triggering anaesthetic. There are few places in the world where MH patients can be studied in such high numbers, so while the statistics do not conclusively prove that non-triggering anaesthetics are safe in MH patients, this sort of study provides very useful information for clinicians dealing with MH patients.

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