

Cost-effectiveness Analysis of Stocking Dantrolene in Ambulatory Surgery Centers for the Treatment of Malignant Hyperthermia

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ABSTRACT

Background: Malignant hyperthermia (MH) is a rare hypermetabolic syndrome of the skeletal muscle and a potentially fatal complication of general anesthesia. Dantrolene is currently the only specific treatment for MH. The Malignant Hyperthermia Association of the United States has issued guidelines recommending that 36 vials (20 mg per vial) of dantrolene remain in stock at every surgery center. However, the cost of stocking dantrolene in ambulatory surgery centers has been a concern. The purpose of this analysis is to assess the cost-effectiveness of stocking dantrolene in ambulatory surgery centers as recommended by the Malignant Hyperthermia Association of the United States.

Methods: A decision tree model was used to compare treatment with dantrolene to a supportive care-only strategy. Model assumptions include the incidence of MH, MH case fatality with dantrolene treatment and with supportive care-only. Sensitivity analyses were performed to assess the robustness of the estimated cost-effectiveness.

Results: The estimated annual number of MH events in ambulatory surgery centers in the United States was 47. The incremental effectiveness of dantrolene compared with supportive care was 33 more lives saved per year. The incremental cost-effectiveness ratio was \$196,320 (in 2010 dollars) per life saved compared with a supportive care strategy. Sensitivity analysis showed that the results were robust for the plausible range of all variables and assumptions tested.

Conclusion: The results of this analysis suggest that stocking dantrolene for the treatment of MH in ambulatory surgery centers as recommended by the Malignant Hyperthermia Association of the United States is cost-effective when compared with the estimated values of statistical life used by U.S. regulatory agencies. (**ANESTHESIOLOGY 2014; 120:1333-8**)

MALIGNANT hyperthermia (MH) is a rare autosomal dominant genetic disorder of the skeletal muscle, manifesting as a hypermetabolic response to volatile inhaled anesthetics and succinylcholine. The incidence of MH in the ambulatory surgical population has been estimated to be 0.31 per 100,000, much lower than that of surgical inpatients at 1 per 100,000.¹ First described in humans in the 1960s, MH carried a case fatality rate of 70 to 80% until widespread treatment with dantrolene began in the 1980s.^{2,3}

Dantrolene inhibits the release of calcium from the ryanodine receptor.⁴ Initially used to treat various forms of spasticity, a large multicenter trial published in the 1980s showed that it was also efficacious in reducing mortality attributable to MH episodes, and it currently remains the only clinically accepted treatment for MH.^{3,5} The case fatality of MH is now estimated to be less than 5% primarily because of dantrolene, along with advances in intraoperative monitoring.⁴ Although the occurrence is rare, MH episodes can be severe, and result in death if not appropriately treated with dantrolene.

What We Already Know about This Topic

- A substantial number of patients receive anesthesia care in ambulatory surgery centers
- Malignant hyperthermia is rare, and whether it would be cost-effective to store dantrolene in recommended quantities at these sites *versus* supportive care alone is unknown

What This Article Tells Us That Is New

- Storing 36 vials of dantrolene at every ambulatory surgery center in the United States would save 33 lives per year at an incremental cost-effectiveness ratio of approximately \$200,000 (in 2010 dollars) per life saved, indicating that the recommended guideline is very cost-effective

A large number of patients now undergo surgery in an out-of-hospital setting, such as ambulatory surgery centers (ASCs). According to the National Survey of Ambulatory Surgery conducted by the Centers for Disease Control and Prevention, 40% of all surgeries in the United States in 2006 were performed in ASCs, representing a 300% increase from 1996 to 2006.⁶ In the same time period, the number of hospital-based surgeries remained relatively constant.

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Given the lethality of MH and the difficulty in screening for MH, the Malignant Hyperthermia Association of the United States has issued guidelines recommending that 36 vials of dantrolene be stocked at each ASC where triggering agents are used and be available within 5 min of the diagnosis of MH.* In addition, ASC accrediting bodies (e.g., Accreditation Association for Ambulatory Health Care, American Association for Accreditation of Ambulatory Surgery Facilities, and The Joint Commission) require compliance with the Malignant Hyperthermia Association of the United States recommended stock of dantrolene. However, accreditation is a voluntary process, and the cost of stocking dantrolene in ASCs has been a concern given the rarity of MH episodes and the 3-yr shelf life of the drug. Cost-effectiveness analysis is a useful tool for prioritizing and weighing the benefits of an intervention against its cost, particularly for providers and policy makers with a limited budget. This study was designed to assess the cost-effectiveness of stocking dantrolene in ASCs as recommended by the Malignant Hyperthermia Association of the United States when compared with the values of statistical life (VSL) estimated by U.S. regulatory agencies.

Materials and Methods

A decision tree was created to visualize the natural timeline of a patient who might experience an MH episode in an ASC, with a probability equal to the incidence of MH (fig. 1). Cost-effectiveness is frequently represented as an incremental cost-effectiveness ratio (ICER),⁷ where the difference in costs of two interventions is divided by the difference of their respective effectiveness as shown below:

$$ICER = \frac{(Cost_{with\ dantrolene} - Cost_{without\ dantrolene})}{(Effectiveness_{with\ dantrolene} - Effectiveness_{without\ dantrolene})}$$

Although dantrolene is the treatment of interest for this cost-effectiveness analysis, it is important to note that it is never appropriate to treat an MH episode with dantrolene alone.⁸ Supportive care, such as patient cooling, correction of metabolic abnormalities, and discontinuing triggering agents, should be applied even when dantrolene is administered. The cost of supportive care was therefore set to \$0 in this study. The only cost to be considered is the cost of dantrolene itself; yearly cost of stocking dantrolene was calculated using the 2010 Red Book average cost of a 20-mg vial of dantrolene, which is \$101.25, multiplied by number of vials stocked, and divided by the shelf life of dantrolene of 3 yr⁹:

$$\begin{aligned} & \text{Total annual cost of stocking dantrolene at each ASC} \\ &= \frac{(\text{Cost per dantrolene vial}) \times (\text{Number of vials})}{\text{Shelf life of dantrolene}} \end{aligned}$$

* The Malignant Hyperthermia Association of the United States. Available at: www.mhaus.org. Accessed December 3, 2013.

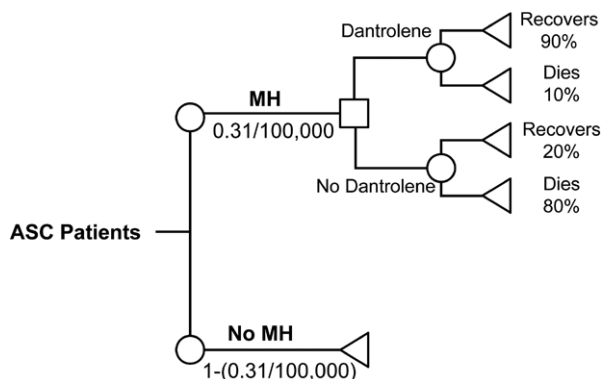


Fig. 1. Decision tree representing the clinical timeline for a malignant hyperthermia (MH) episode in ambulatory surgery centers (ASCs).^{1-3,6,11-16} The square represents a decision node and indicates the choices we are evaluating; in this case whether the ASC administers dantrolene to treat an MH episode. The circles represent chance nodes with each branch having a certain probability of occurring; the sum of the branches from each chance node adds up to 1. There are two possible outcomes: survival or death. The triangles represent terminal nodes indicating the end points of our evaluation.

The estimated annual cost for stocking 36 vials of dantrolene to the ASC was \$1,215. When multiplied by the number of ASCs in the United States (5,316), the total annual cost of stocking dantrolene at all ASCs is \$6,458,940.¹⁰ Effectiveness was measured as number of lives saved using published case fatality rates and number of procedures performed at ASCs per year. The analysis was performed under the following assumptions:

1. The true incidence of MH is uncertain, and thus the number of cases of MH per year is also uncertain. The base case number of 47 MH episodes per annum is the product of the 15 million ambulatory surgical procedures the Centers for Disease Control and Prevention reported for 2006 and the estimated incidence of 0.31 per 100,000 in the patient population undergoing ambulatory surgeries.^{1,6}
2. The true case fatality rate of MH with the administration of dantrolene is unknown. The most cited figure is less than 5%; however, this figure has been challenged, and case fatality rates of 1.4, 4.6, 10, and 11.7% have been cited in the literature.^{1,11-16} A base case fatality rate of 10% was used as a conservative estimate for this study.
3. The true case fatality rate without dantrolene is uncertain. The consensus in the literature is that the case fatality rate of MH before dantrolene was introduced as the standard treatment was as high as 80%.^{2,3}

Cost-effectiveness

A VSL ranging from \$4 to \$10 million was selected as the threshold measure of cost-effectiveness as reported by Kneiser *et al.*¹⁷ This range falls in line with estimates from U.S. regulatory agencies, such as \$7.9 million used by the

Environmental Protection Agency¹⁸ and \$5 million used by the Food and Drug Administration.¹⁹

Sensitivity Analyses

Sensitivity analyses were performed to examine whether the results were robust to changes in the assumptions of the model. ICERs were first calculated by assuming various combinations of the variables in the model. Specifically, we first allowed a range of possible values for one variable while fixing the other variables at base values and then assessed the associations of ICERs with MH case fatality with and without dantrolene treatment, the number of MH episodes per year, and the number of vials of dantrolene. The values for each variable were chosen to represent the plausible ranges in the clinical setting.

In addition to the sensitivity analyses under some selected fixed values, a simulation study was performed to show the distribution of ICERs by assuming a distribution for each variable in the model. Specifically, a Poisson distribution with a mean of 47 and 5,316 was used to generate the count data for number of MH episodes per year and number of ASCs, respectively. A truncated normal distribution with a mean of \$101.25 and an SD of \$25 was assumed for the continuous cost of dantrolene per vial data with the range of the cost to be restricted between \$50 and \$150. A beta distribution with a shape parameter of 2 and a scale parameter of 10 was used to generate MH case fatality with dantrolene treatment, so that the simulated MH case fatality with dantrolene treatment falls between 0 and 68% with a mean at 16.6%. This beta distribution was chosen to reflect our assumption that the MH case fatality with dantrolene treatment is likely to

be around the mean at 16.6% while allowing a wide range of possible values. Finally, a uniform distribution ranging between 70 and 90% was used to generate the continuous MH case fatality without dantrolene treatment. This uniform distribution guarantees that the simulated MH case fatality with dantrolene is always smaller than that without dantrolene. One thousand replicates of the simulation were performed using the statistical software R (R Foundation for Statistical Computing, Vienna, Austria).

Results

The total annual cost of stocking 36 vials of dantrolene at all 5,316 ASCs is \$6,458,940. The incremental effectiveness was 32.9 more lives saved per year [47 × (80% – 10%)]. The base case ICER was \$196,320 per life saved (\$6,458,940/32.9).

The robustness of the base case ICER was assessed in a series of sensitivity analyses (tables 1 and 2; figs. 2 and 3). Treatment with dantrolene became less cost-effective as the case fatality rate with dantrolene treatment increased, or as the case fatality rate without dantrolene decreased, particularly when the number of MH episodes in ASCs was much smaller than the estimated base value (fig. 2). Assuming that the case fatality rate with dantrolene treatment is 10%, the estimated ICER per life saved were \$229,040, \$196,320, and \$171,780, respectively, for case fatality without dantrolene of 70, 80, and 90%. When comparing the ICER with the threshold VSL range of \$4 to \$10 million, the use of dantrolene under base case assumptions remained cost-effective until case fatality with dantrolene treatment reached 78.7%. As the case fatality rate without dantrolene decreased, the

Table 1. ICERs in ASCs under Different Assumptions, with All Other Variables at Base Values

Parameters	Base Value	Range for Sensitivity Analysis	ICER Range
Postdantrolene MH mortality	10%	0–79%	\$171,780–\$13,742,426
Supportive care MH mortality	80%	50–100%	\$343,561–\$152,697
Cost of dantrolene per vial	\$101.25	\$50–\$150	\$96,948–\$290,845
Number of MH episodes per year	47	1–94	\$9,227,057–\$98,160
Vials of dantrolene	36	24,48	\$130,880, \$261,760
Number of ASC	5,316	5,000–10,000	\$184,651–\$369,301

ASC = ambulatory surgery center; ICER = incremental cost-effectiveness ratios; MH = malignant hyperthermia.

Table 2. Distribution of ICERs (in Thousand Dollars) under Different Assumptions

Number Vials of Dantrolene	ICER (\$1,000)				
	1st Percentile	25th Percentile	50th Percentile	75th Percentile	99th Percentile
24	61	107	134	168	328
36	91	161	201	252	496
48	122	214	267	337	652

Assumptions for this simulation study were MH case fatality with dantrolene having a beta distribution (shape parameter = 2, scale parameter = 10), MH case fatality without dantrolene having a uniform distribution (lower bound = 0.7, upper bound = 0.9), cost of dantrolene per vial having a truncated normal distribution (mean = \$101.25, SD = \$25, lower bound = \$50, upper bound = \$150), number of MH episodes per year having a Poisson distribution (mean = 47), and number of ASC having a Poisson distribution (mean = 5,316). One thousand replicates of the simulation were conducted. A percentile indicates the value below which a given percentage of simulated ICERs fall. For example, 99% of simulated ICERs are smaller than \$328,000 for 24 vials of dantrolene. ASC = ambulatory surgery center; ICER = incremental cost-effectiveness ratios; MH = malignant hyperthermia.

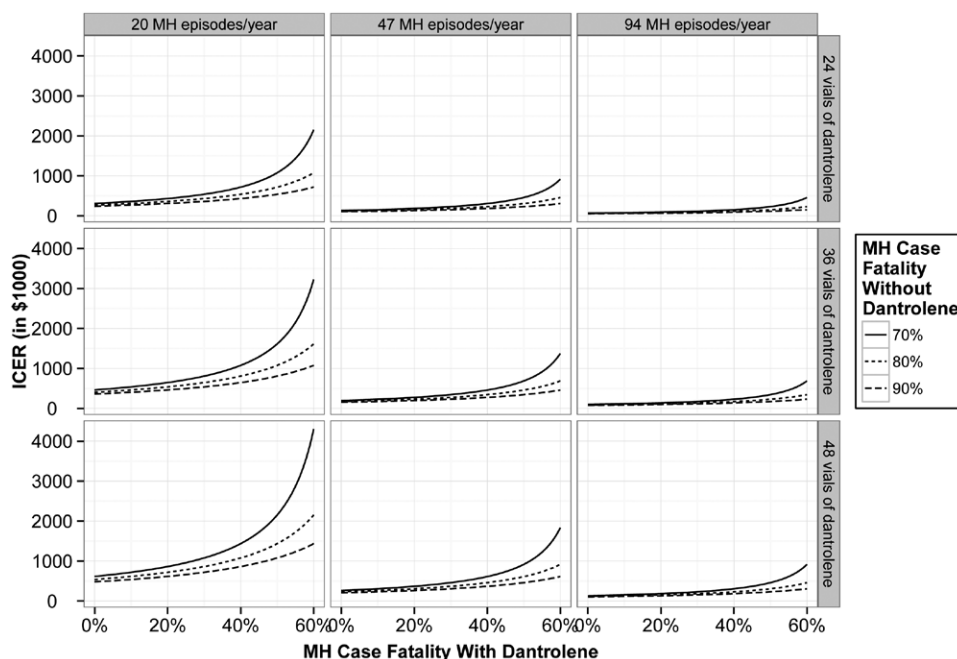


Fig. 2. Sensitivity analysis showing the incremental cost-effectiveness ratios (ICERs) under the assumptions of malignant hyperthermia (MH) case fatality with dantrolene ranging from 0 to 60% given MH case fatality without dantrolene being 70, 80, and 90%, number of MH episodes per year being 20, 47, and 94, number of vials of dantrolene being 24, 36, and 48, cost of dantrolene per vial being \$101.25, and number of ambulatory surgery centers being 5,316.

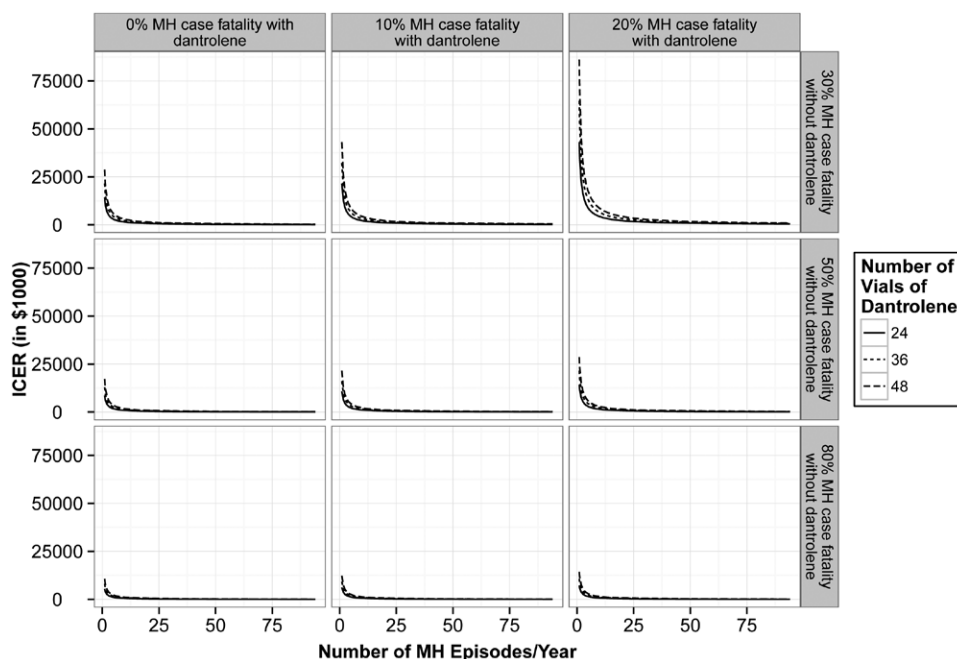


Fig. 3. Sensitivity analysis showing the incremental cost-effectiveness ratios (ICERs) under the assumptions of number of malignant hyperthermia (MH) episodes per year ranging from 0 to 94 given MH case fatality with dantrolene being 0, 10, and 20%, MH case fatality without dantrolene being 30, 50, and 80%, number of vials of dantrolene being 24, 36, and 48, cost of dantrolene per vial being \$101.25, and number of ambulatory surgery centers being 5,316.

ICER became less favorable but still well under the threshold VSL range (table 1).

The case fatality of MH with and without dantrolene treatment and the number of vials of dantrolene were also

subjected to sensitivity analysis (fig. 3). The only scenario under which stocking dantrolene in ASCs would not be cost-effective was when the case fatality of MH with dantrolene treatment was 20% or higher, the case fatality of

MH without dantrolene treatment was 30% or lower, and the annual number of MH episodes in ASCs was 8 or less, 12 or less, and 17 or less for 24, 36, and 48 vials, respectively (fig. 3). The simulation study also showed that stocking dantrolene for the treatment of MH in ASCs would be cost-effective, where 99% of the simulated ICERs were below \$328,000, \$496,000, and \$652,000 for 24, 36, and 48 vials, respectively (table 2).

Discussion

The Malignant Hyperthermia Association of the United States guidelines have recommended that all facilities have at least 36 vials of dantrolene on the premises, but it is unknown how many ASCs are compliant given the cost of the drug and the rarity of MH. However, it is known that the number of outpatient surgeries have been increasing, and therefore exposure to triggering agents is also increasing.^{6,8} It is also known that without dantrolene, an MH episode can be rapidly fatal.⁸ Our results indicate that stocking the recommended number of vials of dantrolene at all ASCs would be cost-effective compared with the estimated VSL used by U.S. regulatory agencies. VSL estimates are derived from a combination of wage-fatality risk and price-risk studies. Simply put, VSL estimates consider tradeoffs between risks to health or mortality and the cost either to reduce exposure to the risks or the money required to accept jobs with inherent risks of mortality or decreased health. Using what they report to be improved econometric practices on panel data, Kneiser *et al.*¹⁷ have narrowed the range of VSL estimates to \$4 to \$10 million dollars. As mentioned, this range falls in line with estimates from regulatory agencies such as the Environmental Protection Agency and the Food and Drug Administration.

The paucity of epidemiologic data on MH is a notable limitation of this study. As a result, several assumptions had to be made about the incidence of MH, and the case fatality rates with and without dantrolene. Despite the often cited 5% MH case fatality rate with dantrolene treatment, we used 10% as our base value. However, the base value we chose may not be conservative enough. Rosero *et al.*¹⁶ estimated the MH case fatality in the postdantrolene era to be 11.7% between 2000 and 2005. A Japanese study reported an MH case fatality that dropped to 15% between 1995 and 2005 after dantrolene was introduced.²⁰ However, a specific limitation of the study by Rosero *et al.*¹⁶ was the inability to capture dantrolene usage because of the nature of the administrative database they based their study on. In the study by Migita *et al.*,²⁰ dantrolene dosage given in Japan is less than that given in North America, and administration is likely to be delayed because dantrolene is not always on site. Our study assumes immediate availability and uniform delivery of dantrolene in case fatality rate with dantrolene and, in this scenario, we think that the MH case fatality rate with dantrolene treatment of 10% is a reasonable base value.

The base case assumption for the case fatality rate of 80% without dantrolene was selected based on studies performed before the introduction of dantrolene. However, the true case fatality rate without dantrolene may be lower given increased awareness, advances in intraoperative monitoring, and delivery of supportive care measures. Furthermore, it should be noted that no study has looked at the case fatality rates of MH with or without dantrolene in exclusively the ambulatory surgery setting. Type of anesthetics used and availability of specialized care in the ambulatory surgery setting could threaten the validity of these assumptions. The MH incidence of 0.31 per 100,000 persons reported in the New York/New Jersey ambulatory surgical population was used as the base value.¹ In the absence of national estimates of MH incidence in ambulatory surgery patients, it is unknown how valid and reliable the assumed base value is. The incidence of MH is difficult to determine because it is clinically silent until exposure to triggering agents and, even then, it displays incomplete penetrance.² Running multiple sensitivity analyses allowed our three main assumptions to be subjected to a wide range of values to assess the robustness of our findings. The results of the analyses showed that stocking dantrolene in ASCs would be cost-effective for the plausible ranges of key variables compared with the estimated VSLs used by U.S. regulatory agencies.

The lack of long-term outcome data for MH survivors prevented the calculation of cost-effectiveness in cost per quality-adjusted life year (QALY). QALYs take into consideration disability, morbidity, life-years saved, and other quality of life factors. QALYs also represent the definitive standard in cost-effectiveness analysis with frequently cited thresholds ranging from \$50,000/QALY to \$100,000/QALY.²¹ Because data on post-MH episode morbidity and disability are lacking, average QALY could not be calculated in this study. However, we think that VSLs are an appropriate substitute. Using the average age of an MH patient at 18.3 yr of age, the average life expectancy of 78.7 yr,²² and the conventional upper limit of \$100,000/QALY for cost-effectiveness, this hypothetical patient would have ≈60 QALYs saved equal to approximately \$6 million dollars, which falls within the range of the VSL estimate of \$4 to \$10 million of Kneiser *et al.*¹⁷ Although the VSL does not represent what any one institution is willing to pay per life saved, because we are considering dollars per life saved and all ASCs in the United States, we think this approximation makes the VSL estimate a suitable substitute.

In summary, the results of this study indicate that stocking dantrolene in ASCs is cost-effective when compared with supportive care only and the estimated VSLs used by U.S. regulatory agencies.

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Competing Interests

Dr. Rosenberg serves as a consultant to Eagle Pharmaceuticals (Woodcliff Lake, NJ) and as the president of the Malignant Hyperthermia Association of the United States (Sherburne, NY), for which he receives no compensation. The other authors declare no other competing interests.

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