Cost-benefit Analysis of Maintaining a Fully Stocked Malignant Hyperthermia Cart *versus* an Initial Dantrolene Treatment Dose for Maternity Units

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ABSTRACT

Background: The Malignant Hyperthermia Association of the United States recommends that dantrolene be available for administration within 10 min. One approach to dantrolene availability is a malignant hyperthermia cart, stocked with dantrolene, other drugs, and supplies. However, this may not be of cost benefit for maternity units, where triggering agents are rarely used.

Methods: The authors performed a cost-benefit analysis of maintaining a malignant hyperthermia cart *versus* a malignant hyperthermia cart readily available within the hospital *versus* an initial dantrolene dose of 250 mg, on every maternity unit in the United States. A decision-tree model was used to estimate the expected number of lives saved, and this benefit was compared against the expected costs of the policy.

Results: We found that maintaining a malignant hyperthermia cart in every maternity unit in the United States would reduce morbidity and mortality costs by $3,304,641 per year nationally but would cost $5,927,040 annually. Sensitivity analyses showed that our results were largely driven by the extremely low incidence of general anesthesia. If cesarean delivery rates in the United States remained at 32% of all births, the general anesthetic rate would have to be greater than 11% to achieve cost benefit. The only cost-effective strategy is to keep a 250-mg dose of dantrolene on the unit for starting therapy.

Conclusions: It is not of cost benefit to maintain a fully stocked malignant hyperthermia cart with a full supply of dantrolene within 10 min of maternity units. We recommend that hospitals institute alternative strategies (*e.g.*, maintain a small supply of dantrolene on the maternity unit for starting treatment). **(Anesthesiology 2018; 129:249-59)**

ONE crucial aspect of anesthesiology is finding clinical and systems-based solutions to address rare but potentially catastrophic events. Malignant hyperthermia (MH), a rare autosomal dominant condition that manifests as a hypermetabolic response when exposed to volatile anesthetics and/or depolarizing muscle relaxants, provides one such example. The treatment for MH is well known, and dantrolene treatment has lowered mortality rates from roughly 80% more than 40 yr ago to 10% in current practice.[1] Additionally, complications from MH (disseminated intravascular coagulation, renal dysfunction, cardiac dysfunction, coma, compartment syndrome, and pulmonary edema), which occurs in 20 to 35% of patients, increase markedly for each 10-min delay in dantrolene administration. If dantrolene administration is delayed beyond 50 min, complication rates increase to 100%.[2,3] However, from a systems perspective, the correct approach toward preparing for MH is uncertain. Although there are slight variations on the incidence of MH reported, the generally accepted incidence rate is 5.85 MH cases per 1,000,000 cases using general anesthesia, or 1 in every 170,698 general anesthetic cases.[4–8] Because MH is so uncommon, it is possible that the costs of having immediately available dantrolene may exceed the benefits at the population level, particularly for operating rooms and procedure areas where general anesthesia is uncommonly provided.

What We Already Know about This Topic

- Prompt availability of dantrolene is important for treating malignant hyperthermia and has resulted in lowered mortality rates
- Maintaining a malignant hyperthermia cart and full treatment dose of dantrolene is expensive, particularly for locations with low incidence of malignant hyperthermia, such as labor-and-delivery units

What This Article Tells Us That Is New

- Cost-benefit analysis showed that the costs associated with maintaining a malignant hyperthermia cart with a full dantrolene supply within 10 min of a maternity unit exceeded the benefits
- Modeling suggested that a more cost-effective approach would be to keep just an initial dose of dantrolene on the maternity unit, with a central supply of dantrolene available within 30 min

Understanding the cost-benefit trade-off of providing dantrolene has important policy implications. Indeed, the Malignant Hyperthermia Association of the United States recommends that dantrolene be made immediately available (for administration within 10 min) in operating room areas.[9] This recommendation is cost-effective for sites with a significant number of general anesthetics (*e.g.*, hospitals and stand-alone surgery

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 225. This article has a visual abstract available in the online version.

Submitted for publication January 6, 2017. Accepted for publication March 23, 2018. From the Department of Anesthesiology, Baylor College of Medicine, Houston, Texas (P.T.H.); and Department of Anesthesiology, Stanford University School of Medicine, Stanford, California (B.C., E.C.S., A.M., E.T.R.).

 Anesthesiology 2018; 129:249-59

<zdoi;10.1097/ALN.0000000000002231>

centers).[4] However, maternity units uncommonly use MH–triggering agents. For example, an institution that delivers 6,000 babies a year and has a 30% cesarean delivery rate and a 5% general anesthesia rate will use general anesthesia less than 100 times a year. With the expected MH incidence of 1 case per 170,698 anesthetics, that maternity unit would expect to have a MH case every 1,700 yr. Such a low incidence prompts the question of whether the standard proposed by the Malignant Hyperthermia Association of the United States is necessary for maternity units, because, to meet this standard, many maternity units should have their own MH cart. Although well intentioned, if the costs of maintaining an MH cart exceed its benefits at the population level, the Malignant Hyperthermia Association of the United States standard diverts resources from other initiatives (*e.g.*, the provision of difficult airway equipment) that may have a larger impact on patient safety and maternal mortality or mortality.

To examine this issue, we conducted a cost-benefit analysis to evaluate whether, at the population level, the benefits of maintaining an MH cart in or near maternity units (and therefore available within 10 min) in the United States (instead of relying on MH carts available in other areas of the hospital) exceed the costs associated with this practice. We also evaluated the cost effectiveness of other alternatives such as keeping just the initial dose of the dantrolene on the unit.

Materials and Methods

Cost-benefit Analysis

We used a cost-benefit analysis to estimate the practicality of providing an MH cart for every maternity unit in the United States. Cost-benefit analysis is often used by policymakers and regulators to understand the economics and population-level suitability of a given intervention (*e.g.*, environmental regulations or vehicle safety regulations).[10–12] With a cost-benefit analysis, the mortality benefits of the given intervention are compared against its costs. Because mortality benefits are typically calculated as the number of lives saved, while costs are estimated in dollars, regulatory agencies use a parameter known as the Value of a Statistical Life to convert mortality benefits (in terms of lives saved) to dollar terms. The Value of a Statistical Life has been estimated to range from $4 million to $10 million per statistical life.[11] Thus, assuming a Value of a Statistical Life of $10 million, a given intervention that would save 100 lives per year would only be worthwhile if it cost less than $1 billion (*i.e.*, $10 million times 100) annually.

In our case, we used a cost-benefit analysis to analyze whether the reduced mortality from a policy requiring that every maternity unit in the United States have an MH cart for dantrolene administration would be worth the costs of implementing such a policy. Below, we describe the methods we used to estimate the benefits and costs of this policy.

Policy Benefits

Having an MH cart present in a maternity unit benefits patients to the degree it reduces mortality and morbidity by facilitating earlier administration of dantrolene. Intuitively, the benefits to patients will be larger to the extent that (1) more general anesthetics are performed, and (2) earlier administration decreases complications and improves survival. To evaluate this hypothesis, we used a decision-tree model. These models use probability of events occurring at each point and give estimates for all possible outcomes. We developed a decision-tree model to estimate the reduction in morbidity and mortality from having an MH cart present in each maternity unit in the United States (fig. 1).

The key parameters for this model were: (1) the number of women entering a labor-and-delivery unit, (2) the incidence of births, (3) the incidence of noncesarean delivery obstetric procedures (*e.g.*, postpartum tubal ligations), (4) the incidence of cesarean deliveries, (5) the incidence of general anesthesia for cesarean deliveries, (6) the incidence of general anesthesia for noncesarean delivery obstetric procedures, (7) the incidence of MH for general anesthetic procedures, (8) MH mortality with no delay in dantrolene treatment, (9) MH mortality with no treatment, (10) MH morbidity with no delay in dantrolene treatment, and (11) MH morbidity with no treatment. In general, where there was a range of estimates in the literature, we chose values that would provide the *highest* reduction in mortality. In converting the benefits of maintaining a cart to dollar amounts, we used a Value of a Statistical Life of $10 million per life, the upper end of the range typically used by regulators.[10]

Policy Costs

We determined the costs of maintaining an MH cart by considering three sources of potential cost: (1) the treatment drug (dantrolene); (2) the physical cart and all other nondantrolene cart drug and disposable items; and (3) maintenance of the MH cart. In regards to the costs of dantrolene, the Malignant Hyperthermia Association of the United States recommends stocking either 36 20-mg vials of the older, less concentrated formulation of dantrolene, or 3 250-mg vials of the newer, more concentrated formulation of dantrolene.[9] We estimated that a vial of dantrolene costs $84.* With a shelf-life of 3 yr, this means that the annualized cost of stocking an MH cart with dantrolene is $1,008 ($84 per vial multiplied by 36 vials, divided by the shelf-life of 3 yr). We used the older formulation of dantrolene for this analysis because it is less expensive.

For the cost of the MH cart, we obtained quotes from suppliers, ranging from $1,400 to $3,200.† Because an MH cart is expected to last 10 to 16 yr, we converted these total costs into an annualized cost by assuming an equal depreciation rate over 16 yr, resulting in an annual cost of $87.50 (equals $1,400/16). Other MH cart items as recommended by the Malignant Hyperthermia Association of the United States include general supplies, monitoring

*Purchase price for the pharmacy at Lucile Packard Children's Hospital, Stanford, California.

†We obtained quotes from Armstrong Medical (Lincolnshire, Illinois), Blue Bell Medical (Van Wert, Ohio), Capsa Solutions (Portland, Oregon), and the Harloff Company (Colorado Springs, Colorado).

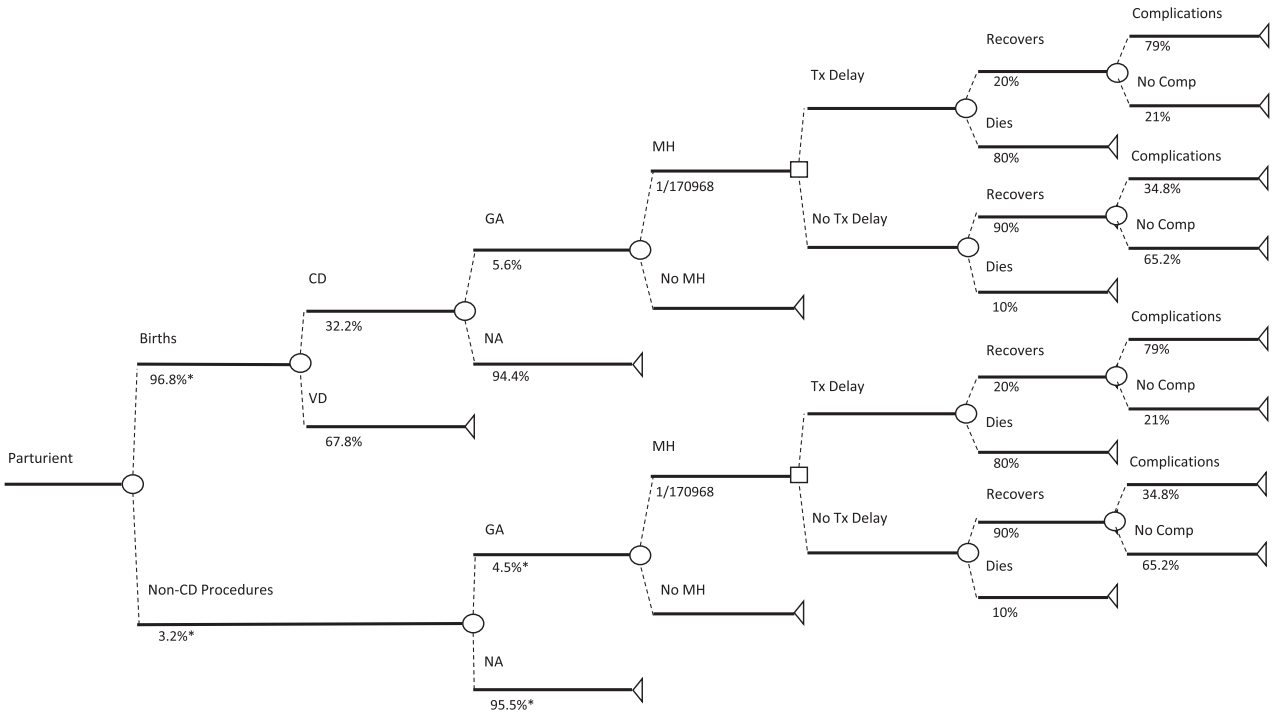

Fig. 1. Decision tree analysis. The decision tree analysis of the various outcomes related to possible exposure to a malignant hyperthermia-triggering anesthetic for a parturient on a maternity unit. A *square* indicates a decision under evaluation. A *circle* represents a chance node with a particular probability of that event happening. A *triangle* represents the terminal node or the final event in the evaluation. An *asterisk* indicates a value obtained from Stanford University Hospital. CD = cesarean delivery; GA = general anesthesia; MH = malignant hyperthermia; NA = neuraxial anesthesia; No Comp = no complications; Tx = treatment; VD = vaginal delivery.

equipment, nursing supplies, lab test supplies, and other drugs that may be useful during resuscitation (including furosemide, sodium bicarbonate, calcium chloride, insulin, and lidocaine).[9] Each individual item in the cart has a shelf life between 1 to 5 yr and was adjusted accordingly to obtain an annual cost (table 1).

The maintenance of MH carts was considered as a cost variable. We assumed that weekly checks of the MH cart is $555 of a registered nurse's time (*i.e.*, 15 min per week times 52 weeks times $42.68 registered nurse hourly wage with benefits as 25% of salary).[13] We estimated that a pharmacist performs, at minimum, monthly checks of MH cart drugs, which has an annual cost of $215 (*i.e.*, 15 min per month times 12 months times $71.68 pharmacist hourly wage with benefits as 25% of salary).[14] The total cost for cart maintenance was therefore estimated to be $770 ($555 + $215).

The cost of a single MH cart was the total of the costs (cost of dantrolene, cost of MH cart and nondantrolene cart items, and MH cart maintenance cost) described above. To ensure compliance with the Malignant Hyperthermia Association of the United States recommendation without ambiguity, we assume all maternity units in each hospital should have an MH cart and therefore multiplied the total estimated cost of a single MH cart by the number of maternity units in the United States. According to data from the fiscal year 2013 American Hospital Association annual survey published in American Hospital Association Hospital Statistics 2015, there are 2,471 hospitals of a total of 4,780 reporting hospitals in the United States that indicated the availability of obstetrics services. The United States has 5,686 registered

Table 1. Abbreviated Malignant Hyperpyrexia (MH) Cart Supply Costs (Excluding the Cost of Dantrolene)

MH Cart Items	Annualized Costs
Other drugs	$66.35
General equipment	$57.72
Monitoring equipment	$15.33
Nursing supplies	$10.48
Lab test supplies	$0.24
MH cart	$87.50
Total	$237.62*

Other drugs included furosemide, sodium bicarbonate, calcium chloride, insulin, and lidocaine; general equipment included vial spikes, angiocaths, T connectors, a 500-ml bag of lactated Ringer's solution, a 500-ml bag of saline solution, sterile injectable water, luer-lock syringes, radial artery catheters, three-way stopcocks, primary intravenous solution sets with drip chambers, 60″ microvolume intravenous extension tubing, pediatric armboards, Salem pump tubes, nonlatex Robinson catheters, catheter-tip syringe, five-in-one connectors, Y connectors, two-way silicone urinary catheters, three-way silicone urinary catheters, peritoneal lavage tray, soda lime canister refill, and ambu bag with mask; monitoring equipment included an arterial line monitoring kit and a central venous pressure line kit; nursing supplies included alcohol prep pads, sterile gauze pads (2×2 and 4×4), iodine prep solution, chlorhexidine prep solution, adhesive dressings, 1″ micropore tape, latex-free tourniquets, urinary catheter insertion kit, and drainage bag with urimeter; and lab supplies included heparinized arterial blood gas syringes and blood tube kits.

*We used cost data from our institution, which obtained the lowest prices of all cart supplies quoted from at least three different vendors.

hospitals.[15] If we assume the rate of obstetric services are the same for the hospitals that did not respond to the American Hospital Association survey, we can reasonably calculate the number of obstetric care hospitals in the United States to be 2,940.

We performed analyses on alternative strategies for maintaining a supply of dantrolene on the maternity unit. First, we eliminated the other supplies (and their costs) from the MH cart except for the dantrolene and analyzed this in the same manner as we did for the complete MH cart. Second, we redid the dantrolene-only analysis without the maintenance costs. Third, we assumed that only an initial dose of dantrolene (250 mg) would be kept on the maternity unit, and the MH cart from a central location would be brought in to complete the MH therapy. We then reanalyzed this scenario for cost benefit using both formulations of dantrolene.

The number of maternal lives saved per year was calculated by multiplying the incidence of MH cases per year by the incremental difference in mortality rate with dantrolene treatment within 10 min. The incidence of MH cases per year equals the number of cesarean deliveries with general anesthetic and noncesarean obstetric general anesthetic cases (*e.g.*, tubal ligations or cerclages) multiplied by the probability of MH per general anesthetic case. The probability of MH per general anesthetic case is 1/170,958,[7] and the total number of annual obstetric cases is 80,427 as calculated by Centers for Disease Control and Prevention and institutional data (fig. 1). Estimated maternal mortality with no dantrolene treatment is 80% and with dantrolene treatment available within 10 min is 10%.[4] The calculated number of annual lives saved is 0.33 (80,427/170,968 times 70% (*i.e.*, 80% minus 10%).

Sensitivity Analysis

We ran a sensitivity analysis to determine how different independent cost variables impact the dependent variable of case fatality rate. We calculated initial cost benefits based on point values for all variables determined from literature and institutional data. With the sensitivity analysis, we determined a range of possible values for each variable to account for clinical plausibility. More specifically, we allowed for a range of values for one variable while keeping all other variables fixed at the base value to determine the cost benefit. In addition to the variables used in the decision-tree model, we included neonatal morbidity and mortality as additional variables in the sensitivity analysis. We used Microsoft Excel Solver (Microsoft, USA) to determine hypothetical values to achieve cost benefit.

To complement the sensitivity analysis, we ran a Monte Carlo simulation. This method randomly chooses a set of numbers for each variable given parameters and plausible distribution of values to determine hypothetical costs while allowing all variables to change simultaneously. We ran 1,000 iterations using the statistical software R (https://www.r-project.org/; accessed April 12, 2018), and each variable was set to have a normal or uniform distribution of possible values based on clinical probability (appendix). For example, in our model, dantrolene had a uniform distribution between $700 and $1,100, and pharmacist salary and benefits had a normally distributed mean of $72 and a SD of $15. Upper and lower limits were applied, and in this case, the pharmacist salary and benefits value could go no lower than $30 and no higher than $100. If the annual cost of the intervention was less than the value of annual lives saved, we would achieve cost benefit.

Results

Figure 1 presents the decision-tree model and parameters we used to estimate the benefit of having an MH cart present in each maternity unit. Overall, our results suggest that having an MH cart present in each maternity unit in the United States would be expected to reduce maternal mortality from 80 to 10%. Stated differently, an MH cart on every maternity unit (available within 10 min) would save 0.33 maternal lives nationally per year. Using a Value of a Statistical Life of $10 million per life, this mortality benefit would be worth $3,300,000 per year. MH morbidity has been well studied, with complications seen in 35% of patients who have an MH crisis,[2] and the risk of MH–related complications increase 2.27 times (or 79%) when the time from the first MH sign and dantrolene administration increases from 10 to 40 min.[16] Costs associated with MH complications would likely require intensive care stays with ventilation and were estimated to be on average $75,000 per stay.[17,18] The cost associated with an increase in maternal morbidity was calculated by subtracting the MH mortality assuming no treatment from the incidence of MH (80,427/170,968 – 0.33 = 0.14) and multiplying that number by the increase in morbidity costs (79% minus 35% times $75,000 = $33,147), which equaled $4,641. Therefore, placing an MH cart in each maternity unit would only be of cost benefit if the cost of doing so nationally was less than the sum of MH morbidity and mortality costs, or $3,304,641 per year.

Our results found that the annual total cost of placing an MH cart in a maternity unit is $2,016: $1,008 for the dantrolene itself, $238 for the cart and nondantrolene items, and $770 for MH cart maintenance. Multiplied by 2,940, the total number of maternity units in the United States would result in a total cost of $5,927,040, which is significantly larger than the $3,304,461 cost-benefit threshold value we calculated.

Neonatal mortality and morbidity were included in the sensitivity analysis and Monte Carlo simulation. Neonatal mortality was calculated by multiplying the probability of maternal mortality or morbidity assuming no treatment, the probable range of values that neonatal death occurs, and the value of a statistical life ([0.33 + 0.06] times 40% minus 0% times $10,000,000). Neonatal morbidity was calculated by multiplying the probability of maternal mortality or morbidity occurring assuming no dantrolene treatment, the probable range of values of neonatal lives not ending in

Table 2. Sensitivity Analyses to Determine the Independent Cost Variables' Impact on the Dependent Variable of Mortality and Morbidity Benefit by Cost Categories

				Cost*	
Cost Categories	Base Value	Lower Limit	Upper Limit	Lower Range	Upper Range
Dantrolene	$1,008.00	$700.00	$1,100.00	$5,019,859	$6,195,859
Other cart supplies	$237.62	$100.00	$400.00	$5,520,776	$6,402,776
Pharmacist time	3	1	5	$5,503,901	$6,346,857
RN time	13	10	20	$5,548,985	$6,803,630
Pharmacist salary + benefits (25%)	$71.68	$30.00	$100.00	$5,557,761	$6,175,161
RN salary + benefits (25%)	$42.68	$25.00	$75.00	$5,249,840	$7,160,840
Number of hospitals	2,940	2,471	3,377	$4,980,140	$6,806,124

*Cost = estimated yearly cost per maternal and fetal lives saved by maintaining a malignant hyperthermia cart on a maternity ward.
RN = registered nurse.

death, the probable range of values of requiring a stay in the intensive care unit, and the cost of the intensive care unit stay ([0.33 + 0.06] times (1 – [40% minus 0%]) times 50% minus 10% times $75,000).[19]

The sensitivity analyses are shown in tables 2 and 3. The analysis found no mortality benefit in all but two categories within clinically plausible variations in our base values. In comparison to the lowest plausible cost of the MH cart, we would achieve cost benefit if general anesthesia rates were nearly doubled or if the incidence of MH in general anesthetic cases was twice as high, *i.e.*, 1 in every 85,484 general anesthetic cases. Neonatal mortality and morbidity were not key drivers of the cost-benefit analysis. Additionally, a more sophisticated analysis with the Monte Carlo simulation, which included both maternal and neonatal morbidity and mortality, found that we did not achieve cost benefit in 93% of the 1,000 iterations, *i.e.*, the annual cost of maternal and neonatal lives saved is less than the cost of having the MH carts in maternity units in 93% of the iterations (tables 4 and 5; appendix).

We analyzed the general anesthetic rates of cesarean deliveries to determine the rate required to achieve cost benefit. If cesarean delivery rates in the United States remained at 32% of all births, the general anesthetic rate would have to be greater than 11% to achieve cost benefit (fig. 2). In addition to general anesthetic rates, cesarean delivery rates and the number of deliveries per hospital were potential drivers in the model; therefore, we also determined possible scenarios that would achieve cost benefit by changing three variables: cesarean delivery incidences, general anesthetic rates, and number of deliveries per hospital (fig. 2). For example, if a unit has 5,000 deliveries and a cesarean delivery incidence of 40%, general anesthetic rate of at least 2% would be required to achieve cost benefit.

We also evaluated the mean annual costs of maintaining a less than fully stocked MH cart and ran Monte Carlo simulations on the various configurations (tables 4 and 5). Reducing the cart content to just dantrolene without the other supplies needed in an MH resuscitation reduced the mean annual costs by less than 20% and was still cost ineffective 85% of the time. Eliminating the maintenance costs from the analysis reduced the cost by more than 50% and made stocking dantrolene cost effective 74% of the time. However, this scenario ignores the true costs of maintaining the supply. Keeping a single vial of the new formulation of

Table 3. Sensitivity Analyses to Determine the Independent Cost Variables' Impact on the Dependent Variable of Mortality and Morbidity Benefit by Effectiveness Categories

				VSL*	
Effectiveness Categories	Base Value	Lower Limit	Upper Limit	Lower Range	Upper Range
Dantrolene intervention MH mortality	10%	1.40%	11.70%	$3,700,857	$3,217,928
30-min dantrolene treatment delay	80%	50%	100%	$1,891,045	$4,235,360
GA rate for CD	5.80%	3.00%	10.00%	$1,823,364	$5,509,039
GA rate for non-CD procedures	4.51%	2%	8%	$3,161,956	$3,486,287
Rate of non-CD procedures	3.20%	2%	4%	$3,204,348	$3,361,121
Number of births	3,988,076	3,988,076	3,988,076	$3,297,634	$3,297,634
Rate of CD of all L&D visits	32.20%	15.00%	42.00%	$1,666,388	$4,227,065
Number of GA cases per MH case	170,968	341,936	85,484	$1,648,817	$6,595,269
Fetal mortality		0%	40%	$3,297,634	$4,864,306
Fetal morbidity		10%	50%	$3,298,880	$3,303,862

Cost benefit is achieved when VSL is greater than lowest cost value.
*VSL = estimated yearly maternal and fetal value of statistical lives.
CD = cesarean delivery; GA = general anesthesia; L&D = labor and delivery; MH = malignant hyperthermia; VSL = value of a statistical life.

Table 4. Distribution of Cost per Annual Life Saved under Different Assumptions

Cost in Dollars per Annual Life Saved				
1st Percentile	25th Percentile	50th Percentile	75th Percentile	99th Percentile
$1,305,711	$2,568,546	$3,366,010	$4,314,678	$7,076,445

Table 5. Distribution of Cost per Annual Life Saved under Different Assumptions

Category	Mean Annual Cost	Percentile
MH cart + maintenance	$5,946,891	93rd
Dantrolene + maintenance	$4,865,075	85th
Dantrolene only (newer formulation)	$3,382,355	50th
Dantrolene only (older formulation)	$2,599,472	26th
Starter pack (older formulation) only	$938,698	0th

Assumptions for this simulation study were normal distributions for salaries and general anesthesia rates and uniform distributions for cost of dantrolene, cost of cart and supplies, number of hospitals, rates of malignant hyperthermia mortality with dantrolene and delay in dantrolene treatment, rates of cesarean and noncesarean delivery procedures, incidence of malignant hyperthermia cases per year, fetal morbidity, and fetal mortality. The upper and lower bounds are shown in the appendix. In total, 1,000 iterations of the simulation were conducted. The mean annual cost for the malignant hyperthermia cart, 36 dantrolene vials, and 13 20-mg vials for a starter pack for the simulation was calculated. The percentiles for cost per annual life saved were determined and indicate the values below which a percentage of simulated costs fall. The values of cost per annual life saved that cross the cost-benefit threshold for the intervention would make the intervention optimal (*e.g.*, mean annual cost for the malignant hyperthermia cart intervention falls in the 93rd percentile, which makes it not optimal 93% of the time, and the mean annual cost for the starter pack falls in the 0th percentile, which makes it optimal 100% of the time).

MH = malignant hyperthermia.

dantrolene[20] on the maternity unit (this vial contains enough dantrolene to start the treatment of a 100-kg patient) without adding maintenance costs is more expensive than keeping a full supply of the older formulation and was cost effective 50% of the time in the Monte Carlo simulations. The only cost-benefit plan when considering maintenance of the supply was to keep a "starter pack" of the older formulation on the maternity unit (13 20-mg vials; enough for the first dose of a 100-kg patient). This plan was cost beneficial 100% of the time in the Monte Carlo simulation.

Discussion

In this study, we performed a cost-benefit analysis to determine the value of maintaining a separate MH cart on the maternity unit within hospitals in the United States. Using conservative assumptions of costs, rates of general anesthesia, incidence of MH, and expected mortality and morbidity from MH, we found that the cost of a life saved is significantly greater than what is considered of cost benefit. Only by assuming an unreasonably high case fatality rate, general anesthetic incidences, or cesarean delivery rates does it become of cost benefit to maintain a fully stocked MH cart on a maternity unit. Our results are primarily driven by the low number of general anesthetics and therefore the extremely low likelihood of an MH incident among parturients. For example, a previous study found that stocking dantrolene is of cost benefit in a small ambulatory surgical center that performs 10 triggering anesthetics a day (*i.e.*, 2,000 to 3,000 anesthetics per year).[4] However, the number of triggering anesthetics is at least an order of magnitude lower in maternity units. For example, even a maternity unit with 10,000 deliveries per year would be expected to perform at most 200 to 300 general anesthetics per year.

Our assumption that mortality per MH case will increase from 10 to 80% if dantrolene is not stocked on the maternity unit is conservative, and the resultant increased mortality rate estimate is probably excessive. The 80% value is the same as no-dantrolene treatment, not delayed treatment (*i.e.*, greater than 10 min from diagnosis). We assumed the same mortality rate as no-dantrolene treatment because we do not know how much mortality is affected by delayed treatment of unknown duration. We cannot make a data-based recommendation for the maximal allowable time to deliver dantrolene to the maternity unit.

In calculating the costs, we have included labor costs to maintain the MH carts, which were not included in a previous dantrolene cost-benefit study.[4] However, labor costs fall under the category of opportunity costs (costs associated with opportunities forgone due to the use of resources), which are widely accepted to be included in cost-benefit analyses.[21] We believe it is necessary to depict all costs related to stocking the cart in the maternity unit.

In calculating the benefits, we used the highest Value of a Statistical Life that is typically used for cost-benefit analysis. The sensitivity analyses and Monte Carlo simulations further demonstrated no cost benefit in all cases when considering maternal morbidity and mortality alone, despite conservative ranges of general anesthesia and cesarean deliveries. General anesthetic rates for cesarean delivery have declined significantly over the years, with the most recently reported national rate to be 6%.[22] Lower general anesthetic rates are encouraged, and should optimally should be less than 1% for scheduled cases. Additionally, national bodies emphasize bringing cesarean delivery rates lower, ideally below the current national levels of 32%.[23,24] Therefore, we doubt there are any maternity units that perform enough cesarean deliveries with general anesthesia in the United States to justify the presence of an MH cart on the unit. However, maternity units with extremely high cesarean delivery rates (*e.g.*, 50%) combined with unacceptably high general anesthesia rates (*e.g.*, 50%) will have an MH incidence an order of magnitude higher than the average unit, and it is likely of cost benefit for them to have an MH cart in their maternity unit.

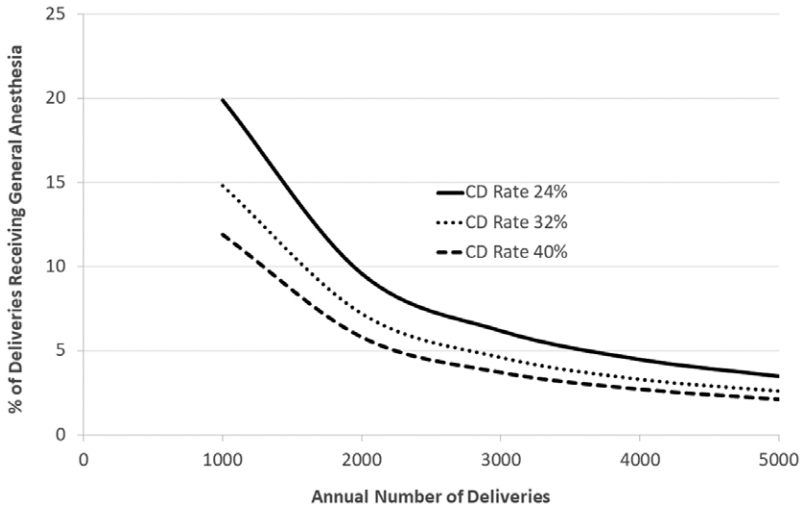

Fig. 2. Cost benefit when changing cesarean delivery incidences, general anesthetic rates, and number of deliveries per hospital. The *lines* on the graph show the points at which the cost of maintaining a malignant hyperthermia cart on a maternity unit equals the value of a statistical life. The *x* axis is the number of deliveries per year, and the *y* axis is the percentage of deliveries that have a general anesthetic. Each *line* represents a different cesarean delivery (CD) rate. Points below the lines are cost-ineffective.

We did not include the more concentrated dantrolene formulation (Ryanodex) in our cost-benefit analysis of a complete MH cart, but given the additional cost of these drugs over dantrolene, they would be expected to be of even less cost benefit. Our assumption is that most maternity units that perform cesarean deliveries are proximate to a central supply of dantrolene that can be brought to the unit within 30 min of a decision to treat MH. We acknowledge that some maternity units may be remote from a central supply location for dantrolene. In these situations, a unit should have their own MH cart. We also assumed the incidence of MH in obstetric patients receiving general anesthesia is the same as general surgical patients. It may be that with the more dynamic nature of a maternity unit, a family history of MH may be missed more frequently than in other settings.

There is a paucity of data on the risks to the fetus, and there are no reported cases of neonatal harm after maternal exposure. We could only find three case reports of MH associated with cesarean deliveries in which there was information on the fetus.[25–27] In only one case was there possible evidence that MH had been triggered in the baby, and we could find no case reports of neonates requiring treatment with dantrolene. In all likelihood, if a neonate ever presented with MH triggered from *in utero* exposure, treatment would likely take place in the neonatal intensive care unit, and the presence of dantrolene on the maternity unit would not affect neonatal outcome. Additionally, detrimental effects of maternal hemodynamic instability on the neonate before delivery would be unaffected by the presence of dantrolene on the unit because the baby would likely be delivered before dantrolene could be administered. Nonetheless, we included neonatal mortality and morbidity in the sensitivity analyses and Monte Carlo simulations. Despite applying conservatively high estimates of neonatal mortality (estimates of up to 40% of neonates dying) and morbidity (including up to 50% of neonates would incur intensive care unit costs), no cost benefit was achieved in 93% of the simulated cases.

Our analysis shows that maintaining an MH cart on the maternity unit, *versus* readily available within the hospital, is not of cost benefit. The MH cart also requires storage space in maternity units that may impact access and workflow in patient-care areas. The money saved from not maintaining a separate and complete MH cart in a maternity unit could be used to purchase more expensive formulations of dantrolene that can be reconstituted faster and potentially make up for the time it takes to retrieve dantrolene from a centralized supply location within the hospital but remote from the maternity unit.[20]

Our analysis implies that keeping an initial dose of dantrolene on the maternity unit may be more cost beneficial than relying on a centralized MH cart for managing a case of MH. The Malignant Hyperthermia Association of the United States recommends an initial dose of dantrolene of 2.5 mg/kg; therefore, 250 mg will be needed to treat a 100-kg patient. One vial of the newer, more concentrated formulation is 250 mg. Alternatively, a vial of the older version of dantrolene contains 20 mg, and 13 vials are required to supply enough for the initial dose for a 100-kg patient. This alternative plan would eliminate the costs of maintaining a cart and reduce the necessary dantrolene stocked on the obstetric unit. Our analysis of this option was found to be cost beneficial with the older formulation of dantrolene and was only cost beneficial 50% of the time with the newer dantrolene formulation (Ryanodex, USA) (tables 4 and 5). We did not include maintenance in this option because the drug could be added to the stock of other emergency supplies kept on the unit (*e.g.*, intralipid for treatment of local anesthetic systemic toxicity), and maintaining the small stock of

dantrolene would not add much to the cost of maintaining the other emergency supplies. This option lowers the costs substantially, reduces storage space, and reduces labor.

The question remains whether the higher cost of the newer dantrolene formulation is offset by the lower footprint of storing one vial *versus* 13 vials of the older dantrolene formulation on the maternity unit. Each vial of the older dantrolene formulation is 60 ml, and almost 1 l of sterile water is required to reconstitute the 13 vials. The newer dantrolene formulation requires just 5 ml of water for reconstitution. Clearly, it would be easier to keep a supply of the new version of dantrolene in an emergency kit on labor and delivery. However, each vial of the new version costs $3,000 and has a shelf life of 33 months. The older version costs $84 for vial and has 36-month shelf life. Therefore, the cost of the first dose of the older dantrolene formulation is one third of the cost of the new dantrolene formulation. The only scenario that is 100% cost effective is to keep a starter kit of the old version.

There are likely to be some maternity units that have a dantrolene supply close enough to their operating room suite so that they meet Malignant Hyperthermia Association of the United States recommendations, or they may perform their cesarean deliveries in the main operating rooms of the hospital. The existence of these situations does not change our results. If we remove a maternity unit because it is capable of using a nearby dantrolene supply, we must reduce a proportionate probability that a general anesthesia–related delivery would occur, and thus it would cause a similar reduction of MH occurrence. Although there are variations of general anesthetic rates among different maternity units, we do not anticipate a reduction that favors maternity units that use main operating room MH carts as opposed to maternity units who should have their own MH cart. Total costs will decrease, but this also results in a proportional decrease in number of lives saved due to the reduction in MH cases and general anesthetics in the maternity units. The results of the analysis and its interpretation therefore stays the same.

The number of maternity units in the United States would only affect the analysis if it was much lower than our derived number of 2,940 and would therefore result in lower associated costs. We performed a sensitivity analysis where we accounted for the variability of the number of maternity units in the United States. According to the American Hospital Association Hospital Statistics, there were a total of 2,471 registered hospitals that responded to the survey and stated that they had obstetric services. In our sensitivity analysis, we set a lower limit of plausibility and assumed that the additional 906 hospitals that did not respond to the survey did not have obstetric services. We found that maintaining MH carts on a fewer number of maternity units was still not cost beneficial.

In conclusion, maintaining a fully stocked MH cart with dantrolene in a maternity unit is not cost beneficial. If general anesthesia rates remain relatively low on maternity units, MH treatment plans that rely on a centralized MH cart are the most cost-beneficial solution in the labor and peripartum setting. We believe that the standards set by the Malignant Hyperthermia Association of the United States can be fulfilled if a hospital demonstrates the ability to rapidly deliver an MH cart to the maternity unit within 30 min of a decision to treat MH and the maternity unit maintains an initial dantrolene treatment dose of 250 mg.

Research Support

Supported by the Foundation for Anesthesia Education and Research's (Schaumburg, Illinois) 2015 Medical Student Anesthesia Research Fellowship program (to Dr. Ho) and funding from the National Institute on Drug Abuse (Bethesda, Maryland; K08DA042314), consulting fees unrelated to this work from Egalet, Inc. (Wayne, Pennsylvania), and the Mission Lisa Foundation (Tampa, Florida; to Dr. Sun).

Competing Interests

The authors declare no competing interests.

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Appendix: R Program Code for Monte Carlo Simulation

For each variable, 1,000 data points are randomly assigned in a normal or uniform distribution. Variables with normal distributions that have a lower and upper bound will contain 1,200 data points initially. Then the first 1,000 data points within the lower and upper bounds will be selected for the simulation.

1. Variables to Calculate Cost
d = total cost of 36 dantrolene IV mg vials
MHcart = malignant hyperthermia cart cost
PT = pharmacist's time in hours required for malignant hyperthermia (MH) cart maintenance
PS = pharmacist's salary and benefits
PS2 = dummy variable of PS, which satisfies specified constraints
RT = registered nurse's time in hours required for MH cart maintenance
RS = registered nurse's salary and benefits
RS2 = dummy variable of RS, which satisfies specified constraints
H_num = number of hospitals in the United States that have labor-and-delivery suites
Tot_Cost = total annual cost of MH cart, MH cart maintenance, and labor-and-delivery nurse training

dantrolene IV 20 mg
uniform distribution within limits
lower bound = $700, upper bound = $1,100

> d ≤ runif(1,000, 700, 1,100)

MH cart supplies
uniform distribution
lower bound $300, upper bound = $450

> MHcart ≤ runif(1000, 300, 450)

pharmacist's time for cart maintenance
uniform distribution with bounds
lower bound = 1, upper bound = 5

> PT ≤ runif(1,000, 1, 5)

pharmacist's salary + benefits
normal distribution
mean = $71.68, SD = $15

> PS ≤ rnorm(1,200, 71.68, 15)
> PS2 ≤ PS [PS ≥ 30 and PS ≤ 100] [1:1,000]

registered nurse's time for cart maintenance
uniform distribution with bounds
lower bound = 10, upper bound = 20

> RT ≤ runif(1000, 10, 20)

registered nurse salary + benefits
normal distribution
mean = $42.68, SD = $10, lower bound = 25, upper bound 75

> RS ≤ rnorm(1,500, 42.68, 10)
> RS2 ≤ RS[RS ≥ 25 and RS ≤ 75] [1:1,000]

number of hospitals
uniform distribution
lower bound = 2,471, upper bound = 3,377

> H_num ≤ runif(1,000, 2,471, 3,377)

calculating the total annual cost in the United States

> Tot_Cost = ([d + MHcart] + PT*PS2 + RT*RS2)*H_num

2. Variables to Calculate Effectiveness
MH_mort_wd = mortality rate of patients who were administered dantrolene immediately
MH_mort_ddelay = mortality rate of MH patients who had a delay in dantrolene treatment, variable as multiplier of MH_mort_wd
Mmorb_wd = maternal morbidity with dantrolene treatment
Mmorb_ddelay = maternal morbidity due to delay in treatment
FMorb = fetal morbidity due to delay in maternal MH treatment
FMort = fetal mortality due to delay in maternal MH treatment

GA_CS = rate of triggering general anesthetics used for cesarean sections in the United States
GA_CS2 = dummy variable for GA_CS, which satisfies specified constraints
GA_nonCS = rate of triggering general anesthetics used for admitted labor-and-delivery patients undergoing noncesarean section procedures in the United States
GA_nonCS2 = dummy variable for GA_nonCS, which satisfies specified constraints
nonCS = rate of admitted labor and delivery patients who undergo noncesarean section procedures
rate_birth = rate of births as a proportion of total procedures done at the hospital
total_births = total number of births in the United States
rate_CS = rate of cesarean sections in the United States
Num_GA_CS = total number of triggering general anesthetic cases in cesarean sections seen in the United States
Num_GA_nonCS = total number of triggering general anesthetic cases in admitted labor-and-delivery patients' noncesarean section procedures seen in the United States
Tot_GA = total number of triggering general anesthetic cases in all admitted labor-and-delivery patient procedures
MH_incidence = the incidence rate of MH in patients who are exposed to a triggering general anesthetic
Tot_MH = total number of MH cases per year

MH mortality with dantrolene
uniform distribution within 1.4 to 11.7%
lower bound 1.4%, upper bound 11.7%

> MH_mort_wd ≤ runif(1,000, 0.014, 0.117)

MH mortality with delay in dantrolene treatment
uniform distribution between 50 and 100%
lower bound = 0.5, upper bound = 1

> MH_mort_ddelay ≤ runif(1,000, 0.5, 1)

maternal morbidity with dantrolene treatment
uniform distribution between 30 and 40%

> Mmorb_wd ≤runif(1,000, 0.3, 0.4)

Maternal morbidity due to delay in treatment

uniform distribution between 60 and 100%

> Mmorb_ddelay ≤runif(1,000, 0.6, 1)

fetal morbidity due to delay in maternal MH treatment
uniform distribution between 10 and 50%

> FMorb ≤runif(1,000, 0.10, 0.50)

fetal mortality due to delay in maternal MH treatment
uniform distribution between 10 and 40%

> FMort ≤ runif(1,000, 0.10, 0.40)

general anesthesia rate for cesarean section
normal distribution
mean = 5.8%, SD = 1%, lower bound = 3%, upper bound = 10%

> GA_CS ≤ rnorm(1,200, 0.058, 0.01)
> GA_CS2 ≤ GA_CS[GA_CS ≥ 0.03 and RS ≤ 0.1] [1:1000]

general anesthesia rate for noncesarean section procedures
normal distribution
mean = 4.51%, SD = 1%, lower bound = 2%, upper bound = 8%

> GA_nonCS ≤ rnorm(1200, 0.0451, 0.01)
> GA_nonCS2 ≤ GA_nonCS[GA_nonCS ≥ 0.02 and GA_nonCS ≤ 0.08] [1:1000]

Rate of noncesarean section procedures
uniform distribution
lower bound = 2%, upper bound = 4%

> non_CS ≤ runif(1,000, 0.02, 0.04)

Rate of birth as a proportion of total procedures performed on admitted labor-and-delivery patients
(vaginal birth + birth *via* cesarean section)/total admitted labor-and-delivery patient procedures

> rate_birth ≤ 1-non_CS [1:1000]

number of births in the United States
taken from Centers for Disease Control and Prevention data

> total_births = 3,988,076

rate of cesarean section
uniform distribution
lower limit = 15%, upper limit = 42%

> rate_CS ≤ runif(1,000, 0.15, 0.42)

determining the number of general anesthesia cases per year

> Num_GA_CS = total_births*rate_CS*GA_CS2

>Num_GA_nonCS=(non_CS/[rate_birth/total_births])*GA_nonCS2
> Tot_GA = Num_GA_CS + Num_GA_nonCS

incidence of MH per year

> MH_incidence = 1/170968
> Tot_MH = Tot_GA * MH_incidence

3. Variables to Calculate Cost Benefit
Yearly_Maternal_Life_Saved = the incremental number of lives saved per year by having the dantrolene immediately available in the labor-and-delivery suite
Yearly_Maternal_Mortality_Value = yearly value of maternal life saved
Yearly_Maternal_Morbidity_Value = yearly value of maternal morbidity cost saved
Yearly_Fetal_Mortality_Value = yearly value of fetal life saved
Yearly_Fetal_Morbidity_Value = yearly value of fetal morbidity cost saved
Total_Annual_Values_Lives_Saved = yearly value of maternal and fetal lives saved by having dantrolene immediately available

>Yearly_Life_Saved=Tot_MH*(MH_mort_ddelay−MH_mort_wd)
>Yearly_Maternal_Mortality_Value=Yearly_Life_Saved*10,000,000
> Yearly_Maternal_Morbidity_Value = (Tot_MH- Yearly_Life_Saved)*(Mmorb_ddelay – Mmorb_wd)*75,000
> Yearly_Fetal_Mortality_Value = (Yearly_Life_Saved + Mmorb_ddelay – Mmorb_wd)*FMort*10,000,000
> Yearly_Fetal_Morbidity_Value = (Yearly_Life_Saved + Mmorb_ddelay – Mmorb_wd)*(1-FMort)*FMorb*75,000
> Total_Yearly_Value_Lives_Saved = Yearly_Maternal_Mortality_Value + Yearly_Maternal_Morbidity_Value + Yearly_Fetal_Mortality_Value + Yearly_Fetal_Morbidity_Value

Cost benefit is achieved if Total_Yearly_Value_Lives_Saved > Tot_Cost

Results of Monte Carlo simulation:

Tot_Cost
Mean $5,946,891
Minimum $3,896,981
Maximum $9,216,903

Total_Yearly_Value_Lives_Saved
1st percentile: $1,446,511
25th percentile: $3,117,773
50th percentile: $4,093,143
75th percentile: $5,361,656
85th percentile: $5,928,065
99th percentile: $8,470,213