**Supplemental Digital Content 6. Question 2, (Query 6): Does the administration of succinylcholine without concomitant volatile anesthetic administration trigger MH?**

Additional records identified through other sources (Cochrane and EMBASE)
(n =19)

Records identified through PubMed database searching
(n =398)

Full-text articles excluded, with reasons (co administration of volatile
(n = 29)

Records excluded (abstract revealed not using succinylcholine alone)
(n =182)

Records after reviews (75), and non-English abstracts or full article (101), and duplicates (19) removed
(n = 223)

## Included

## Eligibility

## Screening

## Identification

Studies included in qualitative synthesis
(n = 11)

Full-text articles assessed for eligibility
(n =40)

Records screened
(n =222)

**Literature Summary:** The literature reported 21 MH events following the administration of succinylcholine without exposure to volatile anesthetic agents; 18 in the US or Canada. For 12 of these cases, succinylcholine doses were 0.5−2.5 mg/kg. At least 10 patients received clinically indicated dantrolene. Of 21 cases meeting eligibility criteria, 12 experienced MH morbidity including rhabdomyolysis, renal dysfunction, life threatening arrhythmias, and change in consciousness levels. There were no reported deaths in eligible cases. All articles have reporting bias due to selective reporting.

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| Article Identifier/Database Source | Number of Succinylcholine without volatile MH cases | Description of cases | Dantrolene Use/Indication | MH Morbidity/Mortality | OCEBM Level of Evidence | Number of fulminant or CGS>20 | Comments |
| Visoiu M1, Young MC, Wieland K, Brandom BW.Anesthetic drugs and onset of malignant hyperthermia. Anesth Analg. 2014 Feb;118(2):388-96.  | 5 cases (of 477 patients)succinylcholine dose unknown | 1 had fulminant MH-age 14 y (CGS 73), 4 had possible MH (CGS 28, 40, 40, 43) 16 y, 26 y, 71 y, 45 y. 1 case began in ED, 1 case in delivery room, 2 cases began in OR, 1 case began in PACU. All in hospitals in US or Canada. No CHCT or molecular genetic testing reported.  | 5 received dantrolene/judged clinically indicated after examination of AMRA forms by MGL/BWB/SR | 1 case of renal dysfunction and change in consciousness level/no mortality | 3 |  5 (2 case~~s~~ overlap with those of Anesth Analg 2010 Feb 1;110(2):498-507) | Reporting bias |
| Klingler W, Heiderich S, Girard T, Gravino E, Heffron JJ, Johannsen S, Jurkat-Rott K, Rüffert H, Schuster F, Snoeck M, Sorrentino V, Tegazzin V, Lehmann-Horn F. Functional and genetic characterization of clinical malignant hyperthermia crises: a multi-centre study.Orphanet J Rare Dis. 2014 Jan 16;9:8.  | 2 cases (of 200 patients) | 1- ENT surgery, 13M, isolated MMR.IVCT positive, and genetics positive (p.R614C)2- Testicular torsion, 10M, MMR and hyperthermia IVCT positive, genetics negative | Not mentioned. Dantrolene in case #2 would have been indicated. No details are available to determine if it was given. | Case#1 developed rhabdomyolysis | 3 | 1 | Biased. Only patients who survived made it to referral center.  |
| Schuster F, Johannsen S, Schneiderbanger D, Roewer N. Evaluation of suspected malignant hyperthermia events during anesthesia. BMC Anesthesiol. 2013 Sep 23; 13(1):24.  | 3 cases (out of 19) | CGS scores: 15, 40, 15.All were IVCT positive and negative genetics.One showed neurogenic myopathy in histopathology | Used in one case.Dantrolene was indicated in fulminant case (CGS=40) and given. | Fulminant case developed rhabodmyolysis. | 3 | 1 | Biased. Only patients who survived made it to referral center. |
| Riazi S, Larach MG, Hu C, Wijeysundera D, Massey C, Kraeva N. Malignant hyperthermia in Canada: characteristics of index anesthetics in 129 malignant hyperthermia susceptible probands.Anesth Analg. 2014 Feb; 118(2):381-7.  | 20 cases (of 129 patients) | CGS: 15-60Succinylcholine doses for the 20 cases ranged from 0.5 to 2.5 mg/kg. All were CHCT positive and 7 carried causative *RYR1* mutations. | 4 patients received dantrolene. This treatment was indicated.  | 3 cases (2 met the inclusion criteria) developed life threatening arrhythmias. 7 cases ( all met inclusion criteria) developed rhabdomyolysis. One of these also had life threatening arrhythmia | 3 | 12 (succinylcholine doses for these 12 patients ranged from 0.5 to 2.5 mg/kg) | Biased. Only patients who survived made it to referral center. |
| Lavezzi WA, Capacchione JF, Muldoon SM, Sambuughin N, Bina S, Steele D, Brandom BW. Case report: Death in the emergency department: an unrecognized awake malignant hyperthermia-like reaction in a six-year-old. Anesth Analg. 2013 Feb;116(2):420-3.  | 1 case report6M | Awake MH (rigidity, hyperthermia), resulted in cardiac arrest in ER after succinylcholine.Carried pathogenic *RYR1* variant (p.G4820W). |  | Death | 4 | Not counted | - |
| Pulnitiporn A1, Charuluxananan S, Inphum P, Kitsampanwong W. Malignant hyperthermia: a case report in Thai Anesthesia Incidents Study (THAI Study).J Med Assoc Thai. 2005 Nov;88 Suppl 7:S149-52. | One (case report)3M | Rigidity, hypercabia, tachycardia,Hyperthermia, AcidosisCGS: 58 | No dantrolene was used, but its used would have been indicated. | Developed rhabodmyolysis /Patient survived.. | 4 | 1 fulminant case |  |
| Larach MG, Gronert GA, Allen GC, Brandom BW, Lehman EB. Clinical presentation, treatment, and complications of malignant hyperthermia in North America from 1987 to 2006.Anesth Analg. 2010 Feb 1;110(2):498-507.  | 2 cases (of 284 patients) | CGS: 40, and 73 | Both received dantrolene and its use was indicated. | No MH morbidity or mortality | 3 | Both cases were also reported in Anesth Analg 2014:118(2):388-96] Not counted because duplicate |  |
| Ording H. Incidence of malignant hyperthermia in Denmark.Anesth Analg. 1985 Jul;64(7):700-4.  | 17 cases (11.8%) Succinylcholine-only | No detailed information. The cases were NOT fulminant but were all aborted cases. | Not mentioned | No details. | 3 | 0 | - |
| Lazarus A, Rosenberg H. Malignant hyperthermia during ECT. Am J Psychiatry. 1991 Apr;148(4):541-2. | One (case report)30MaleECT2 previous uneventful anesthetics | Rigidity, Hyperthermia, and tachycardiaCHCT was positive | NO dantrolene was used although its use would have been indicated. .  | No MH morbidity or mortality. | 4 | 1 fulminant case |  |
| Jones R, Shahid F, Cowell RP. An unusual case of malignant hyperthermia presenting on the acute medical take.Br J Hosp Med (Lond). 2015 Feb;76(2):110-1. | 63M for panendoscopy | Initial generalized rigidity.Delayed rhabdomyolysis with single dose of succinylcholine (presented with CK= 42000, pH:7.23, PCO2:62 mmHg, 4 hours after use).Positive IVCT. Pathology showed central cores. | No dantrolene was given. | Developed renal failure requiring hemodialysis. | 4 | 0 (post discharge case) | - |
| Gokhale YA, Marathe P, Patil RD, Prasar S, Kamble P, Hase NK, Agrawal MB, Deshmukh SN, Menon PS. Rhabdomyolysis and acute renal failure following a single dose of succinylcholine.J Assoc Physicians India. 1991 ;39(12):968-70. | 33M for tympanoplasty | 1.5 mg/kg succinylcholine. Myoglobinuria 6 hours postopNot tested. | Not mentioned | Developed renal failure. | 4 | 0 | - |
| **Summary of Literature Cases:** deleted non-anesthetic triggered MH (Lavezzi et al. and cases that could not be examined due to non-English language) |  |  | 10 received dantrolene that was clinically indicated | 12 eligible cases were associated with MH complications. No deaths in eligible cases. |  | **21** (18 from US or Canada) |  |
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| **Anesthesia Closed Claims Project MH cases** triggered by succinylcholine without volatile anesthetics from U.S. cases with an event year between 1970 – 2014 (not reported in any published references or to NAMHR). | 30F for emergency Cesarean section in hospital in 1984. | Three doses of succinylcholine. Death in mother; newborn survived. | 1 fulminant case with dantrolene indicated and given after examination of AMRA forms by MGL/BWB/SR  | 1 MH death | 3 | **1** fulminant case (US and does not overlap with other literature cases cited above) | Reporting bias  |
| **NAMHR MH cases** triggered by succinylcholine without volatile anesthetics from 2013-2016 (not reported in any of the published references above) | 2 cases triggered in a hospital | CGS 43, 58No CHCT or genetic testing was done. | 2 cases received dantrolene that was indicated and given after examination of AMRA forms by MGL/BWB/SR. | 2 cases with morbidity (decreased level of consciousness) likely due to MH /no mortality | 3 |  2 cases that did not overlap with other cases cited above.  | Reporting bias |

AMRA: Adverse metabolic/musculoskeletal reactions to anesthesia, CGS: Clinical grading scale, CHCT: Caffeine-halothane contracture test, CICR: calcium-induced calcium release, CK: Creatine Kinase, ECT: Electroconvulsive therapy, ED: Emergency Department, F: Female, IVCT: in vitro contracture test, M: Male, MH: Malignant hyperthermia, MMR: Masseter muscle rigidity, NAMHR: North American Malignant Hyperthermia Registry of MHAUS, OR: operating room, PACU: post-anesthesia care unit, TIVA: Total intravenous anesthesia.

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