Medications and doses used in Medical Assistance In Dying: A National Retrospective Cohort Study

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Abstract

***Background*:** There is little evidence describing the technical aspects of an assisted death, including medications, doses, and complications.

***Methods*:** We conducted a retrospective cohort study of patients who received MAID using data from the Office of the Chief Coroner for Ontario supplemented with chart data from three Canadian centers. We used a parametric survival model for multivariate analysis to identify relationships between medications, doses, and time from procedure start until death.

***Results*:** The cohort consisted of 3557 patients, with a mean age of 74 (SD 13) years, 49.8% were female, the majority (72%) having a diagnosis of cancer, with the remainder having cardiovascular/respiratory or neurologic disease. Approximately 45% of patients died in hospital, 49% in the home, and 6% in hospice. The most commonly used medications were midazolam (91%), propofol (99%), and rocuronium (93%). Median time from injection until death was 9 [IQR 6] minutes. Lidocaine (any dose) and high-dose propofol were associated with prolonged time from injection until death. The use of cardiotoxic agents (bupivacaine, potassium chloride) were associated with reduced times until death. Complications occurred in 41 (1%) of MAID deaths, mostly related to venous access or need for a second medication administration.

***Interpretation*:** In a large sample of patients who died with medical assistance, certain medications were associated with small differences in times from injection to death and ccomplications were rare. More research is needed to identify the medication protocols which predictable outcomes consistent with patient and family expectations for an assisted death.

Introduction

A growing number of countries have decriminalized medical assistance in dying (MAID) as a means for patients to avoid prolonged suffering(1-4). While the practice of MAID varies across jurisdictions, it can include voluntary euthanasia, in which a health care provider directly administers lethal medications, or assisted suicide, in which a lethal medication is made available to the patient for self-administration(5). Implementation of MAID varies across geographical areas in Canada and many parts of Europe, both voluntary euthanasia and assisted suicide are used; Colombia uses voluntary euthanasia only; and Switzerland, the Australian state of Victoria, and several US states permit assisted suicide only(5-8).

Though nearly 7000 Canadians have died with medical assistance, there is scarce literature on the technical aspects of providing MAID, as the current literature predominantly explores the ethical issues, eligibility of MAID, and the impact on patients, families, and health care providers(2,9,10). While the Canadian Association of MAID Assessors and Providers (CAMAP) has released a guidance document for IV administration, limited data exists on the specific medications, doses, timing of administration and complications occurring during clinician-administered MAID(11). Reported complications from jurisdictions outside Canada include difficulty obtaining IV access, longer-than-expected time to death, pain on injection, and need for a second MAID medication kit(1,12). These reports indicate complications during medication administration can cause further patient suffering and distress for families and clinicians(1,10, 13). Choice of medication and technique of administration may play an important role in ensuring a comfortable and dignified death. Our study aimed to describe the medications used in MAID, their impact upon time until death, and the rates of complications, in order to optimize the technical aspects of providing MAID.

Methods

Data Sources

This study was reviewed and approved by the Hamilton Integrated Research Ethics Board (HIREB #7902). We performed a retrospective cohort study using de-identified data from the Office of the Chief Coroner for Ontario's MAID Database, which includes information on all Ontarians who have died with medical assistance. As the database from the Office of the Chief Coroner recorded timing of medication administration only up to the end of 2018, we used data from records at three high-volume centers (Hamilton Health Sciences [Hamilton, Ontario], The Ottawa Hospital [Ottawa, Ontario], and Vancouver Costal Health [Vancouver, British Colombia]) to provide information on IV drug administration timing from 2019 onwards, as these centres' documentation for MAID included information on the timing of medications used when providing MAID (Figure 1).

We collected data on patient characteristics (age, gender, and diagnosis), the location of MAID (home, hospital, or hospice/palliative care facility); type of MAID provider (nurse practitioner, physician specialty); the medications and doses used, and complications. Data regarding physician specialty and setting of MAID provision were not available for patients from Vancouver, Canada. We excluded records for which complete medication dosage and timing data was unavailable or for which oral medications were used for MAID.

Outcomes

The primary outcome measure was length of time until death, starting from the administration of the first medication, as achieving a painless rapid death is a primary objective of MAID. Secondary outcomes included factors associated with complications of MAID, defined as need for a secondary MAID kit, pain or burning on administration, or loss of intravenous access.

Statistical Analysis

Data from the chart review were documented in a Microsoft excel file. Binary data were summarized as counts and percentages. Continuous variables were summarized with mean and standard deviation (SD) or median and inter-quartile range (IQR), as appropriate. Univariate analysis was conducted using the log-rank test to identify factors that had a significant association with survival time. A multilevel mixed-effects parametric survival model with Weibull distribution was used for multivariate analysis to account for the hierarchal structure of the data (Figure 1). The multivariable model was built using a combination of statistical metrics (likelihood ratio test) and clinical expertise. Variables included the administered medication types: pre-medication (typically midazolam), analgesic (typically lidocaine) anesthetic (propofol and phenobarbital), paralytic (rocuronium and cisatracurium), and cardiotoxic (bupivacaine and potassium chloride). As medications were generally given at a few discrete standard dosages, if used, they were categorized into "low," "standard," and "high" dosages, rather than treated as a continuous variable (Table 1). The multivariable model was adjusted for age, sex, and primary care provider (nurse practitioner [NP] vs medical doctor [MD]). We conducted a complete case analysis and performed a post-hoc sensitivity analysis excluding patients with time until death exceeding one hour, as deaths exceeding one hour were judged by the investigators to be exceedingly long and could impact the relationship between medication and timing of death. The data were analyzed using Stata, version 16 (StataCorp), using $P < 0.05$ as the threshold for statistical significance.

Results

Demographics

We analyzed 3557 adult patients (mean [SD] age, 74 [13] years, range 22 to 105 years) who received MAID between 2016 to 2020. Patient genders were balanced, 50.2% (1786/3557) male and 49.8% (1770/3557) female. Patients and treatment characteristics are reported in Table 2. 88% (3113/3357) of the patients included in the study were from Ontario, 16% (444/3557) were from British

Columbia. Cancer was the most prevalent primary diagnosis for patients receiving MAID (72%), followed by cardiovascular/respiratory (24%) and neurological (4%) disease. The location of MAID was divided into three broad categories: hospital setting; hospice/palliative care facility; or community/other. Community and other was defined as private residence, retirement home, long-term care, and complex care centers. Most patients received MAID in the hospital (45%) or in the community (49%). Only 6% of patients received MAID in a dedicated palliative care facility.

Medications Used in MAID

The IV medications and the dosages used to perform MAID are summarized in Table 3. Midazolam was the most common pre-medication sedative used in the provision of MAID, received by 91% of patients (median dose 10 mg; IQR = 10 mg; range 0-70 mg), though a few patients received metoclopraminde (n=4). 70% (2477/3557) of patients received lidocaine as an analgesic (median dose 40 mg; IQR 20; range 2-1000); one received magnesium sulphate as an analgesic. 21 patients received an opioid (morphine, hydromorphone, or fentanyl). In regard to anaesthetic medications, 85% (2999/3538) of the patients received propofol 1000 mg (median 1000 mg; IQR 0; range 1-3000 mg), while four patients in the entire sample received phenobarbital, all at a dose of 3000 mg. Rocuronium was the most commonly used paralytic, with 81% (2832/3486) of the reported sample receiving a dose of 200 mg (median 200, IQR 0; range 10-400 mg). Of those receiving cisatracurium, 98% (252/258) received a dose between 30 to 40 mg. 24% (863/3557) of patients received cardiotoxic medications, most commonly bupivacaine (n = 582; median 400 mg; IQR 0; range 20-2000). Only 4% of patients received potassium chloride (n=129, median 80 mEq; IQR 0; range 10-1000 mEq).

Length of MAID

The median (IQR) length of time from the initiation of MAID until death was nine minutes (IQR = 6)**.** The shortest documented MAID procedure was one minute, and the longest documented MAID was

121 minutes. In univariate analysis, we used Kaplan-Meier survival curves for each medication used in MAID to explore which medications were associated longer deaths (Appendix Figure 1). The median survival increased from nine to 12 minutes when patients received high dose propofol compared to the standard dose ($p < 0.001$). Patients who received low and standard doses of lidocaine had a median survival time of 9 and 10 minutes respectively, compared to the eight minutes median survival for those who did not receive any lidocaine (Figure 1). The median difference in procedure time between patients who did not receive any bupivacaine and those that received low, standard, and high doses was one minute. Patients who received a standard dose of potassium chloride had a median survival of two minutes less than those who did not receive potassium chloride. The median length of MAID was increased by four, two, and one minute in those who received low and standard dose midazolam compared to those who did not receive midazolam at all.

The Kaplan-Meier survival estimates were plotted against the log of time and followed a linear trend which indicated the Weibull model was appropriate for the data. Results from the multivariate analysis are reported in Table 4. After adjusting for the other medications, high dose propofol maintained a statistically significant relationship with length of time from medication administration until death (hazard ratio [HR] = 0.4; $p \leq 0.001$, 95% CI = 0.3 to 0.7). In multivariate analysis, patients who received lidocaine were associated with having prolonged lengths of MAID compared to those who did not receive lidocaine as part of the MAID medication regimen (low dose lidocaine HR = 0.8, $p = 0.097$, 95% CI = 0.6 to 1; standard dose lidocaine HR = 0.6, $p < 0.001$, 95% CI = 0.6 to 0.7; high dose lidocaine = 0.8, $p = 0.009$, 95% CI = 0.7 to 0.9). In regard to the paralytics, the standard dosages of cisatracurium and rocuronium were associated with the same effect on the length of MAID (standard cisatracurium dose HR = 1.0, $p = 0.661$, 95% CI = 0.9 to 1). The most commonly used cardiotoxic, bupivacaine 400mg intravenous (n = 429), was associated with shorter MAID times (HR = 1.2, $p = 0.013$, CI = 1 to 1.3). Standard dose of potassium chloride was not associated with shorter MAID time (HR = 1.2, $p = 0.197$, CI = 0.9 to 1.4).

Sensitivity Analysis

A survival analysis excluding patients with death timing longer than one hour was conducted (n= 2,566). There was no difference in the associations between length of MAID and dosages used except for potassium chloride. After removing patients with greater than one hour from first injection until death, the relationship was statistically significant (HR = 1.5, $p < 0.001$, CI = 1.2 to 1.9).

Complications

There were 41 complications reported, after review, the reported complications fell into one of two main categories. The most common complication documented was related to obtaining IV access or loss of IV access after initiating the procedure (n = 23). Sixteen of 2570 patients experienced prolonged time to death requiring a second kit. There were no reported complications related to the specific medications used in the provision of MAID, and insufficient number of complications to assess association with provider type or setting of MAID.

Discussion

To our knowledge, this study is the first large cohort evaluating medications, dosages and complications of MAID in Canada. The population included in the study is similar to that described across Canada and elsewhere, with an older population, roughly equal gender balance, and cancer being the most prevalent diagnosis among those who receive MAID(14-15). As expected, based upon previous literature review and CAMAP guidance documents, midazolam

was the only sedative used, lidocaine was the most common analgesic, propofol was the most common anesthetic, and rocuronium was the most common paralytic(1,11).

High-dose propofol and rocuronium were counter-intuitively associated with a longer time until death. This may be because higher doses of these medications were used in cases where an initial injection was thought to be inadequate, either due to reduced effectiveness or concerns about IV placement. It is also possible the prolonged time to death with high-dose propofol is due to unreported or unrecognized technical complications, as clinicians used a second backup kit without it being reported as a complication. Alternatively, the higher dose of medication may take longer to inject and thus increase the duration of the procedure.

Lidocaine was also associated with longer duration between initial injection until death. Patients that received lidocaine took on average approximately one minute longer to die than those who did not receive lidocaine. This could be for several reasons. It could be due to procedural factors, such as the increased time needed to inject and flush the medication itself, or because clinicians concerned about discomfort, administer lidocaine and infuse propofol more slowly. It may also be due to the anti-arrhythmic effects of lidocaine, which could prolong the time until cardiac arrest(16). Pain on injection was a very rare complication (n = 2), either due to underreporting or low incidence. If the latter, it suggests lidocaine may not be necessary, and contributes to a short, but potentially unnecessarily prolonged time until death.

While cardiotoxic agents were used in a minority of MAID provisions, it appears their use is associated with hastened death. Potassium chloride decreases the membrane resting potential of cardiac cells, thus preventing myocardial repolarization and bupivacaine blocks sodium channels throughout the heart and leads to acute conduction disturbances. In our study, there was an association between both cardiotoxic agents, bupivacaine and potassium chloride

and a shortened time until death. The relationship between bupivacaine and time until death was statistically significant in both the primary and sensitivity analysis.

Reassuringly, reports of adverse events were rare. The complications in this cohort were mainly related to intravenous access. Identifying patients who may have potentially difficult vascular access prior to the initiation of MAID and then acquiring the most skilled providers to insert the intravenous line may minimize unnecessary discomfort. As the dataset was repurposed for analysis, it is possible other technical complications (e.g. patient discomfort, seizures, anaphylaxis) were not reported or captured in this analysis. As the Office of the Chief Coroner for Ontario routinely speaks with patients' families after a MAID death, any major complications unrecognized by clinicians may be reported by families, and these would have been captured in the dataset. Thus, it is reassuring that complications are either very uncommon or insufficiently troubling to clinicians, patients, and families to even be recognized as such.

Our study has several strengths, including the its large and multicenter sample, which increases the generalizability of our findings. However, several limitations must be considered. First, as a retrospective cohort study, unmeasured confounding limits any inferences of causation regarding the effects of the medications used in MAID. Second, the clinical information was collected and repurposed for this retrospective cohort study, as such, the data were at risk for errors during data collection and extraction phases. The lack of standardization of data collection by clinicians across sites in the Office of the Chief Coroner database may have resulted in underreporting of complications, despite mandatory reporting to the Office of the Chief Coroner for patients in Ontario.

This study primarily describes MAID care in Canada. In order to effectively evaluate the therapies used to perform MAID and the patient experience, the outcomes evaluated must be

defined as importance to patients and their families. To the investigators' knowledge, there is no patient reported outcome measure evaluating the technical quality of MAID from the patient and family perspective, though efforts are ongoing(17, 18). Future research should explore patient preferences including the preferred length and setting for a "good death" in the context of MAID, to ensure clinicians use medications which result in predictable outcomes consistent with patient and family expectations for an assisted death.

Table 1. Categorization of dosages

	Dosage range	N
Midazolam (mg)		
None	0	192
Low dose	1 to 9	122
Standard dose	10 to 19	1595
High dose	> 19	661
Lidocaine (mg)		
None	0	420
Low dose	1 to 39	67
Standard dose	40 to 60	1849
High dose	> 60	239
Cisatracurium (mg)		
None	0	2389
Low dose	1 to 29	1
Standard dose	30 to 40	159
High dose	> 40	3
Rocuronium (mg)		
None	0	163

Low dose	1 to 149	267
Average dose	150 to 200	2108
High dose	> 200	14
Bupivacaine (mg)		
None	0	2041
Low dose	1 to 399	89
Standard dose	400	429
High dose	> 400	11
Potassium Chloride (mEq)		
None	0	2470
Low dose	1 to 79	5
Standard dose	80	90
High dose	> 80	5
Propofol (mg)		
None	0	34
Low dose	< 1000	409
Standard dose	1000	2999
High dose	> 1000	96

Table 2. Baseline Characteristics of MAID patients from 2016 to 2020

	N = 2570
Age	
Mean (sd), yr	74 (13)
Profession – n (%)	
MD	3304 (93%)
NP	240 (7%)
Gender – n (%)	
Male	1786 (50%)
Female	1770 (50%)
Center – n (%)	
Inpatient	1382 (45%)
Hospice or Palliative Care Facility	187 (6%)
Community & Other (e.g. private residence, LTC)	1,537 (49%)
Patient Diagnosis – n (%)	
Cancer	2519 (72%)
Neurological	23 (0.7%)
Cardiovascular/Respiratory	840 (24%)

Other	126 (4%)
Medical Specialty – n (%)	
Family	1391 (49%)
Anesthesia	473 (17%)
Critical Care	95 (3%)
Emergency	96 (3%)
Internal medicine	290 (10%)
Neurology	12 (0.4%)
Oncology	1 (0.04%)
Other	10 (0.4%)
Palliative Care	382 (14%)
Radiation Oncology	31 (1%)
Surgery	47 (2%)

Table 3. Medications and dosages used to perform MAID

Sedative (Midazolam)	**Median**	**IQR**	**min**	**max**
Total	10	10	1	70
% of patients with dose = 0 mg	9%			
Analgesic				
Lidocaine	**Median**	**IQR**	**min**	**max**
Total	40	20	2	1000
% of patients with dose = 0 mg	18%			
Anesthetics				
Propofol	**Median**	**IQR**	**min**	**max**
Total	1000	0	1	3000
Phenobarbital	**Median**	**IQR**	**min**	**max**
Total	1000	0	3000	3000
% of patients with dose = 0 mg	0%			
Paralytics				
Rocuronium	**Median**	**IQR**	**min**	**max**
Total	200	0	10	400
Cisatracurium	**Median**	**IQR**	**min**	**max**
Total	40	10	20	80
% of patients with dose = 0 mg	0%			
Cardiotoxic				

Bupivacaine	**Median**	**IQR**	**min**	**max**
Overall	400	0	20	2000
Potassium Chloride	**Median**	**IQR**	**min**	**max**
Overall	80	0	10	1000
% of patients with dose = 0 mg	76%			

Table 4. Multivariate Survival Analysis of Weibull Parametric Model with Medications and Dosages

	Hazard Ratio	P	95% CI	Median length (sec)*
Lidocaine (ref = no dose)				480
Low dose (1 to 39 mg)	0.8	0.097	0.6 to 1	600
Standard dose (40 to 60 mg)	0.6	< 0.001	0.6 to 0.7	540
High dose (> 60 mg)	0.8	0.009	0.7 to 0.9	480
Propofol (ref = Low dose [Less than 1000 mg**])**				480
No dose	1.4	0.537	0.5 to 1	570
Standard dose (1000 mg)	0.9	0.399	0.8 to 1	540
High dose (> 1000mg)	0.4	< 0.001	0.3 to 0.5	720

Paralytic (ref = Rocuronium standard dose [150 to 200 mg])				540
Rocuronium				
Low dose (1 to 149 mg)	0.9	0.227	0.8 to 1	540
High dose (> 200 mg)	0.4	0.002	0.3 to 0.7	870
Cisatracurium				
Standard dose (30 to 40 mg)	1.0	0.661	0.9 to 1	540
Low dose (1 to 29 mg)	0.8	0.810	0.1 to 5.6	840
High dose (> 40 mg)	0.4	0.124	0.1 to 1.3	1020
Bupivacaine (ref = no dose)				540
Low dose (1 to 399 mg)	1.0	0.672	0.8 to 1.3	480
Standard dose (400 mg)	1.2	0.013	1 to 1.3	480
High dose (> 400 mg)	0.7	0.197	0.4 to 1.2	480
Potassium Chloride (ref = no dose)				540
Low dose (1 to 79 mg)	1.3	0.587	0.5 to 3.5	600
Standard dose (80 mg)	1.2	0.197	0.9 to 1.4	420
High dose (> 80 mg)	0.7	0.391	0.3 to 1.6	840

*unadjusted for covariates

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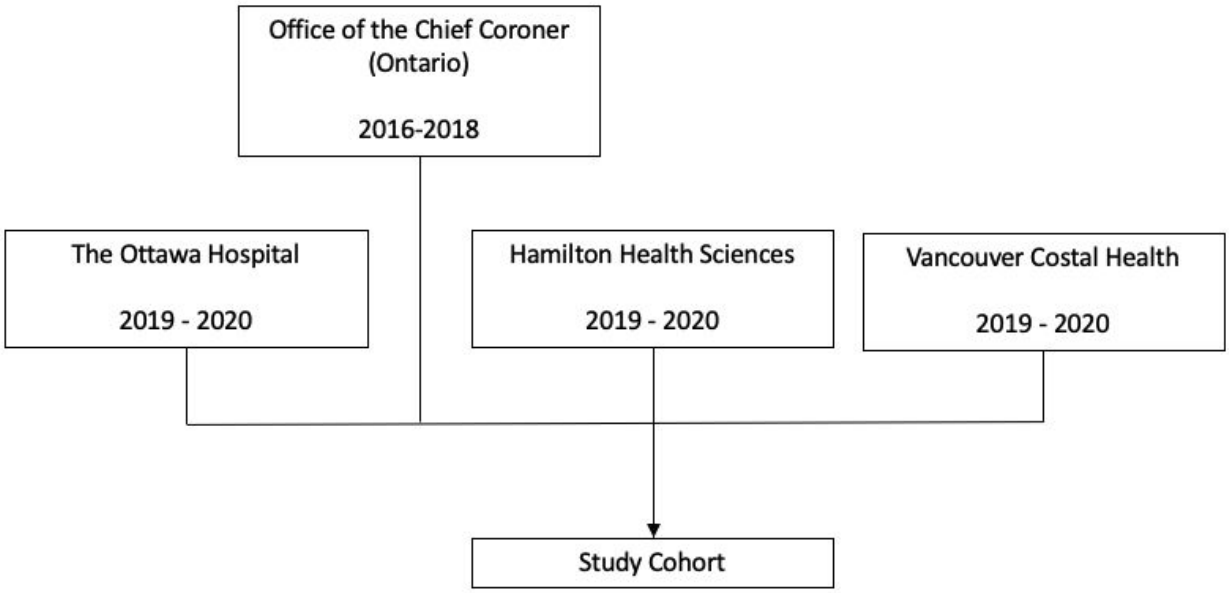
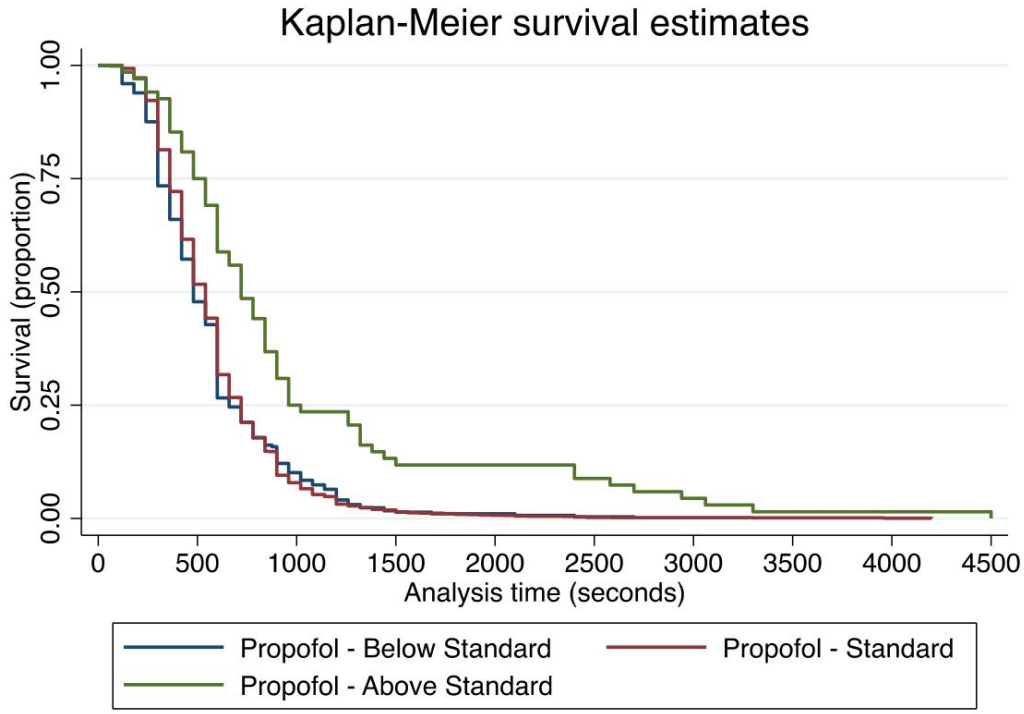


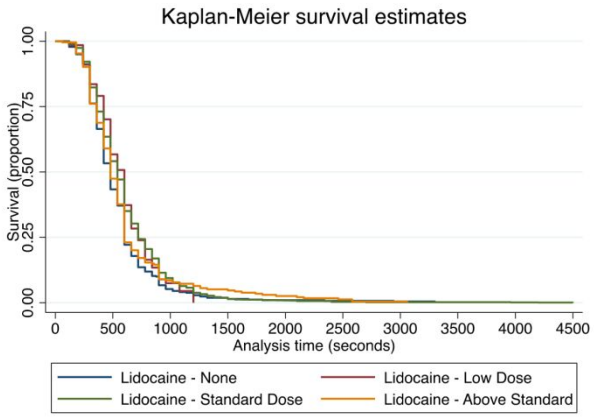
Figure 1. Patient flow diagram



$p < 0.001$

Figure 2. Kaplan-Meier survival curve of mortality comparing difference dosages of propofol

Appendix Figure 1. Kaplan-Meier survival estimates for medications used in MAID



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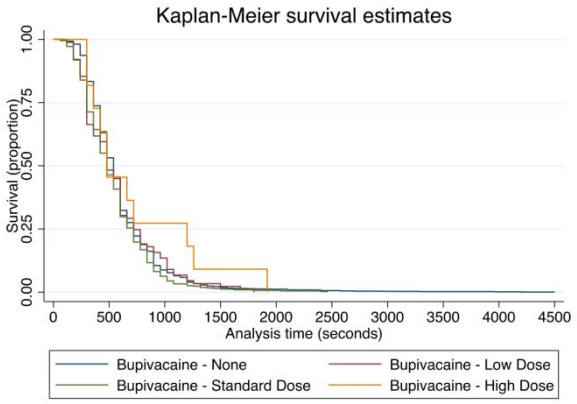

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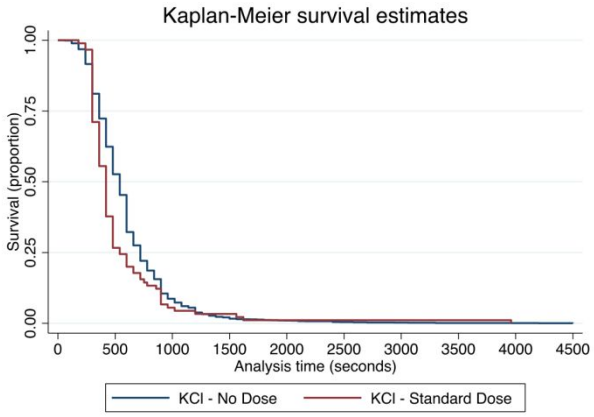

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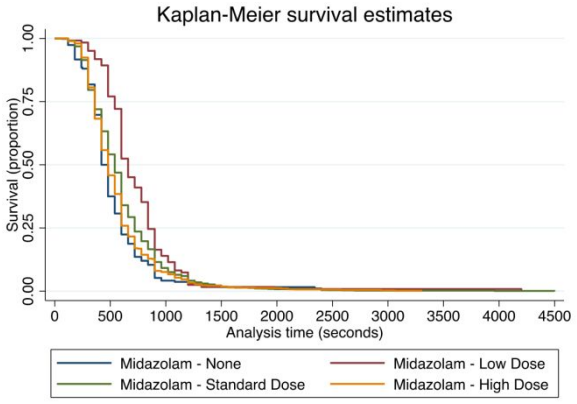
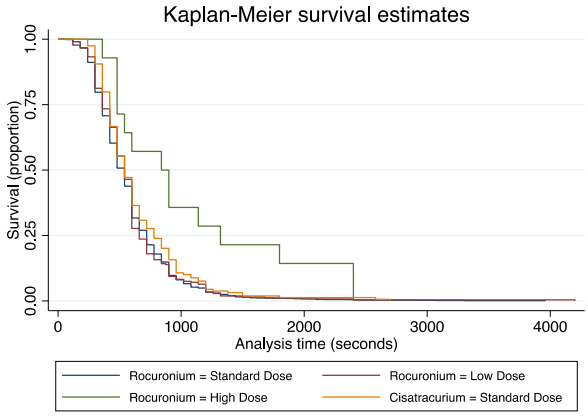


p < 0.001



p = 0.0022

Appendix Table 1. Sensitivity Analysis: Multivariate Survival Analysis of Weibull Parametric Model with Medications and Dosages

	Hazard Ratio	P	95% CI
Lidocaine (ref = no dose)			
Low dose	0.8	0.107	0.6 to 1
Standard dose	0.7	< 0.001	0.6 to 0.8
High dose	0.7	< 0.001	0.6 to 0.9
Propofol (ref = Low dose)			
No dose	Insufficient observations		
Standard dose	1.1	0.343	0.9 to 1.2
High dose	0.4	< 0.001	0.3 to 0.5
Paralytic (ref = Rocuronium standard dose)			
Rocuronium			
Low dose	1.0	0.800	0.9 to 1.1
High dose	0.4	< 0.001	0.2 to 0.6
Cisatracurium			

Standard dose	0.9	0.295	0.8 to 1.1
Low dose	0.7	0.728	0.1 to 5
High dose	0.4	0.075	0.1 to 1.1
Bupivacaine (ref = no dose)			
Low dose	1.0	0.885	0.8 to 1.2
Standard dose	1.2	0.001	1.1 to 1.4
High dose	0.6	0.083	0.3 to 1.1
Potassium Chloride (ref = no dose)			
Low dose	1.3	0.626	0.5 to 3.4
Standard dose	1.5	< 0.001	1.2 to 1.9
High dose	0.6	0.285	0.3 to 1.5