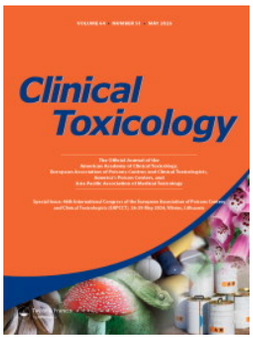

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CLINICAL RESEARCH

Flumazenil use in acute poisoning: improved composite clinical outcomes in a propensity-matched retrospective cohort study

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ABSTRACT

Introduction: Despite being an effective benzodiazepine antagonist, flumazenil is not routinely used in patients with overdose due to the potential risk of major adverse events. Although recent studies have reported a low rate of major adverse events, the benefit of its utility on clinical outcomes remains unclear. This study aims to determine the effect of flumazenil treatment on the clinical outcomes of comatose patients with acute benzodiazepine or nonbenzodiazepine hypnotics poisoning.

Methods: This was a retrospective observational study on consecutive adult patients reported to the Hong Kong Poison Control Centre from 1 July 2008 to 31 December 2024 for benzodiazepine or nonbenzodiazepine hypnotics overdose with Glasgow Coma Scale eight or less. Patients treated with flumazenil, the intervention, were matched with patients in the control group by propensity score matching. The Finkelstein-Schoenfeld method with matched pairs approach was used to compare the primary outcome, a hierarchical composite endpoint consisting of in-hospital death, intensive care unit admission, and length of hospital stay. Secondary outcomes included mechanical ventilation and pneumonia within two days.

Results: A total of 599 patients were included for propensity score matching, and 98 patients in the intervention group and 501 patients in the control group were matched in a 1:1 ratio. Two patients in the intervention group and one patient in the control group died during the in-patient episode of care; the deaths in the intervention group were not attributed to flumazenil. The hierarchical composite endpoint (in-hospital death, then ICU admission, then length of hospital stay) in the interventional group was significantly improved, with a win ratio of 1.68 (95% CI 1.17–2.41). The ICU admission rate (42.9% vs 69.4%, $P<0.001$) and the proportion of patients who received mechanical ventilation (35.7% versus 65.3%, $P<0.001$) was significantly lower in the intervention group. No difference was found in the death, length of stay and occurrence of rapid-onset pneumonia.

Discussion: These results indicate the improvement of primary outcome in the intervention group was predominantly attributed to the reduction in ICU admission and mechanical ventilation. The effect size of flumazenil treatment could be partially offset by the adoption of non-invasive airway management strategy.

Conclusion: Among comatose patients with acute benzodiazepine or nonbenzodiazepine hypnotics poisoning, flumazenil treatment was associated with reduction in ICU admission and mechanical ventilation; as well as a better outcome for the composite endpoint of in-hospital death, ICU admission rate, and length of hospital stay.

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Benzodiazepines; coma; flumazenil; nonbenzodiazepine hypnotics; outcome; overdose

Introduction

Flumazenil is a competitive benzodiazepine antagonist at the gamma-aminobutyric acid ($GABA_A$) receptor; it can rapidly reverse the sedating effect and respiratory depression caused by benzodiazepines [1–3]. Zopiclone, zolpidem and zaleplon are GABAergic hypnotics commonly referred to as the 'nonbenzodiazepine hypnotics'; which exert their sedating effect via a subclass of benzodiazepine receptors and can also be reversed by flumazenil [4]. While benzodiazepines, zopiclone and zolpidem were among the top ten poison exposures reported to the Hong Kong Poison Control Centre (HKPCC) from 2008 to 2020, the use of their antidotes was decreasing [5–9].

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Recommendation by some experts and toxicology textbook on its usage in acute poisoning is limited by the controversial risk-benefit profile [1,10].

Disparity exists in both the reported risks and benefits between historical and more recent studies. In contrast to cases of seizures, cardiac dysrhythmias, and deaths after flumazenil administration reported in the 1990s [11–15], more recent studies have reported concordant findings of a low rate of major adverse events on seizures and deaths [16–18]. On the other hand, no consensus has been reached on the potential benefit of awakening the intoxicated patient from coma. While the abandonment of empirical or diagnostic flumazenil use in patients with unknown drug overdose [19] results in a lower incidence of seizure, concrete evidence on its benefits in reducing diagnostic and therapeutic interventions, as well as length of hospital stay [20–22] is still lacking.

This study aims to determine the effect of flumazenil treatment on mortality, ICU admission and length of stay in patients with coma due to acute benzodiazepine or nonbenzodiazepine hypnotics poisoning. We hypothesize that flumazenil can improve the composite outcome in this group of patients. The secondary objective is to determine whether flumazenil can reduce the number of aspiration pneumonia and mechanical ventilation cases.

Methods

Study design and setting

This was a retrospective observational study on patients reported to the HKPCC between 1 July 2008 and 31 December 2024 for acute benzodiazepine or nonbenzodiazepine hypnotics poisoning with impaired consciousness. The HKPCC is the sole poisoning centre in Hong Kong that provides toxicology consultation services to health care professionals in the city and receives voluntary poisoning cases reporting from 18 local public emergency departments (EDs). Clinical data of the poisoning cases were entered into the Poison Information and Clinical Management System (PICMS) in HKPCC by clinical toxicologists or supervised trainees. Entries were regularly updated and audited to ensure accuracy. This study was approved by the Central Institutional Review Board of the Hospital Authority (reference no. CIRB-2025-588-5). Informed consent was waived because of the retrospective study design and data anonymization. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines in reporting this study [23].

Patient selection

Entries of poisoning cases during the study period were extracted from the PICMS database if they fulfilled all three criteria: 1) age ≥18 years; 2) in-house poison codes of benzodiazepines, nonbenzodiazepine hypnotics, or sleeping pills; and 3) Glasgow Coma Scale (GCS) ≤8. Duplicate entries were excluded. A chart review of medical records retrieved from the Hospital Authority Clinical Management System, an electronic archive of clinical and laboratory data, was performed to determine case eligibility. The exclusion criteria were as follows: 1) not benzodiazepine or nonbenzodiazepine hypnotics acute poisoning; 2) non-local cases; 3) uncertain flumazenil administration for acute toxicity; 4) concurrent acute cerebral injury e.g., traumatic brain injury, intracranial hematoma, and stroke; 5) concurrent surgical emergency e.g., biliary sepsis, traumatic pelvis fracture; 6) concurrent carbon monoxide or opioid toxicity with rapid normalization of GCS after high flow oxygen and naloxone, respectively; 7) cardiac arrest upon ED presentation.

Data collection

The following pre-coded discrete data was abstracted by a built-in automatic electronic export function in the PICMS: age, gender, poison data (ingested poisons and qualitative/quantitative laboratory confirmation of poison exposures), clinical data (clinical features on presentation and investigations results), electrocardiogram (ECG) data (dysrhythmias, prolonged QRS and corrected QT interval), management data (antidotes and other specific treatment) and outcome data. They were entered by HKPCC physicians before the commencement of data abstraction and were not affected by the study. Prolongation of QRS and corrected QT interval on ECGs performed at ED or at time of toxicology consultation was abstracted as pre-coded categorical data. Onset of pneumonia was correlated with radiology reports or chest radiograph findings manually by the principal investigator according to the radiological criteria in US CDC pneumonia definition (supplement content). Details of the intervention (bolus dose, infusion and treatment responsiveness) as well as history of hypnotic dependence were abstracted from accompanying narratives in PICMS and clinical records in Hospital Authority Clinical Management System by the principal investigator.

Definitions

The diagnosis of acute benzodiazepine and nonbenzodiazepine hypnotics poisoning was made by the attending

clinicians or clinical toxicologists of HKPCC who reviewed the case, with or without confirmation of exposure by qualitative liquid chromatography and mass spectrometry of urine samples. Glasgow Coma Scale was assessed and documented by triage nurses or attending clinicians. Hypotension was defined as systolic blood pressure less than 90 mmHg. Tachycardia was defined as a heart rate of more than 100 beats per minute, whereas bradycardia was defined as a heart rate of less than 60 beats per minute. Respiratory failure was defined by either a respiratory rate less than eight per minute, or oxygen saturation less than 90%, or partial pressure of carbon dioxide (PaCO2) more than 6.9 kPa or 51.8 mmHg. Rapid-onset pneumonia was defined as pneumonia that developed within two days of admission. Seizure or dysrhythmia occurring two or more hours after the intervention was considered not temporally related. This time criterion was based on the relatively short half-life of flumazenil [3]. The principal investigator resolved data discrepancies between PICMS and Hospital Authority Clinical Management System and determined the eligibility of individual cases.

Intervention and matching

The intervention under investigation was intravenous flumazenil administration as a means to antagonize the acute toxicity of benzodiazepine or nonbenzodiazepine hypnotics poisoning in the first 24 h after presentation. The decision and timing (in ED, ward or ICU) of flumazenil treatment was at the discretion of the attending clinician with or without prior toxicology consultations. Patients with GCS normalized to baseline within minutes after flumazenil were defined as intervention responders. Partial responders were those with documented improvement in respiration or GCS, but GCS remained ≤13 after intervention. Non-responders were those without improvement in respiration or GCS. The control group included patients who did not receive flumazenil throughout the course of acute care for poisoning. Patients in both the intervention and control groups received routine practice and supportive care for poisoning at the attending clinicians' discretion.

Patients in the intervention group were matched with patients in the control groups in a 1:1 ratio. Propensity score matching method was used to select the matched pairs. The probability of being in the intervention group, i.e., the propensity score, was estimated for each patient by logistic regression using covariates including age, gender, GCS, presence of hypotension, bradycardia, tachycardia, respiratory failure before treatment, presence of vomiting and seizure, types of ingested poison and ECG features. Every patient in the intervention group was matched with a single available patient in the control group according to their propensity score. The balance of covariates between groups in the matched dataset was evaluated using the standardized mean difference and variance ratio for optimizing the propensity score model and matching algorithm.

Outcomes and statistical analysis

The primary outcome was a composite endpoint of in-hospital death, ICU admission and length of hospital stay in hierarchy by their clinical priorities. All composite endpoint components were truncated at 28 days. The length of hospital stay was rounded to the number of days counting from ED attendance. Transferring to non-acute wards or psychiatric units was considered discharge from the hospital. The secondary outcomes included the proportion of patients who received mechanical ventilation, the proportion of patients with pneumonia that developed within two days of admission, and each component in the primary endpoint.

The baseline patient characteristics were described overall and by group. Continuous variables were presented as mean and standard deviation or median and interquartile range (IQR). Student's t-test or Mann–Whitney U test was used to compare continuous variables between groups. Categorical variables were reported as frequencies and percentages. They were analyzed by either chi-square test or Fisher's exact test.

In analysis of the primary endpoint, we used the Finkelstein-Schoenfeld method with matched pairs approach [24,25]. Each patient in the intervention group was compared with each patient in the matched control group, along the hierarchical outcomes in descending order of clinical importance (in-hospital death, then ICU admission, then length of hospital stay), until one showed a better outcome. If a patient from the control group does better, it is called a 'loss'; whereas if the patient from the intervention group does better, it is called a 'win'. When the hierarchy is exhausted without a decisive win or loss, a 'tie' is declared. The primary outcomes were compared using the Mann–Whitney U test. The effect size was described as the win ratio, win odds and net benefit with their associated confidence interval (CI). The win ratio was defined as the number of wins in the intervention group divided by the number of losses, whereas the net benefit was defined as the difference between the proportion of wins and losses in the intervention group. The win odds were similar to win ratio while taking the number of ties into account. Variances and

confidence intervals were calculated using the method described by Dong et al. [26]. The sample size was estimated using the method described by Yu et al. [27]. A minimum sample size of 105 patients in each study group would provide the study with 80% power to detect a win ratio ≥1.6 with 5% proportion of ties in the primary outcome at a two-sided 5% significance level. The secondary outcomes were compared using the chi-square test for binary endpoints and Mann–Whitney U test for continuous endpoints.

The analyses were performed using Statistical Package for the Social Sciences (SPSS) for Windows version 31.0 (IBM Corp., Armonk, NY, USA) and R software version 4.5.1 (The R Project for Statistical Computing) with R package *MatchIt* and *WINS*. Statistical significant was set at a two-sided p-value <0.05.

Results

During the study period, 814 entries were extracted from the PICMS database, four of which were duplicated entries and 211 cases were excluded. Figure 1 shows the flow chart of exclusion. The most common reasons for exclusion were not benzodiazepine or nonbenzodiazepine hypnotics poisoning, followed by documented GCS >8 and predominant opioid toxicity reversed with naloxone. A total of 599 cases were included for propensity score matching analysis. Ninety-eight matched pairs were selected by nearest-neighbour matching without replacement; no caliper was applied for the maximum number of matches. The post-matching standardized mean difference of covariates was similar to the algorithm applying caliper at 0.2 times standard deviation of the logit of the propensity score (supplement content).

The demographic and clinical characteristics of all included cases and matched cohort were shown in Table 1 and Table 2, respectively. Urine toxicology immunoassay or laboratory toxicology screen results were available in 88% and 90% of the control and intervention groups, respectively (Supplementary Table 1). The most commonly ingested benzodiazepines were lorazepam, clonazepam and diazepam (Supplementary Table 2). Among the nonbenzodiazepine hypnotics, zopiclone ingestion was almost twice the amount of zolpidem ingestion (Supplementary Table 3). Only one case of zaleplon ingestion was identified, likely reflecting that the medication is not registered or marketed in Hong Kong. Co-ingestions were identified in most cases among all groups (62.2–75.2%). The three most common classes of poisons were non-tricyclic antidepressants, neuroleptics and alcohols. Intervention characteristics are presented in

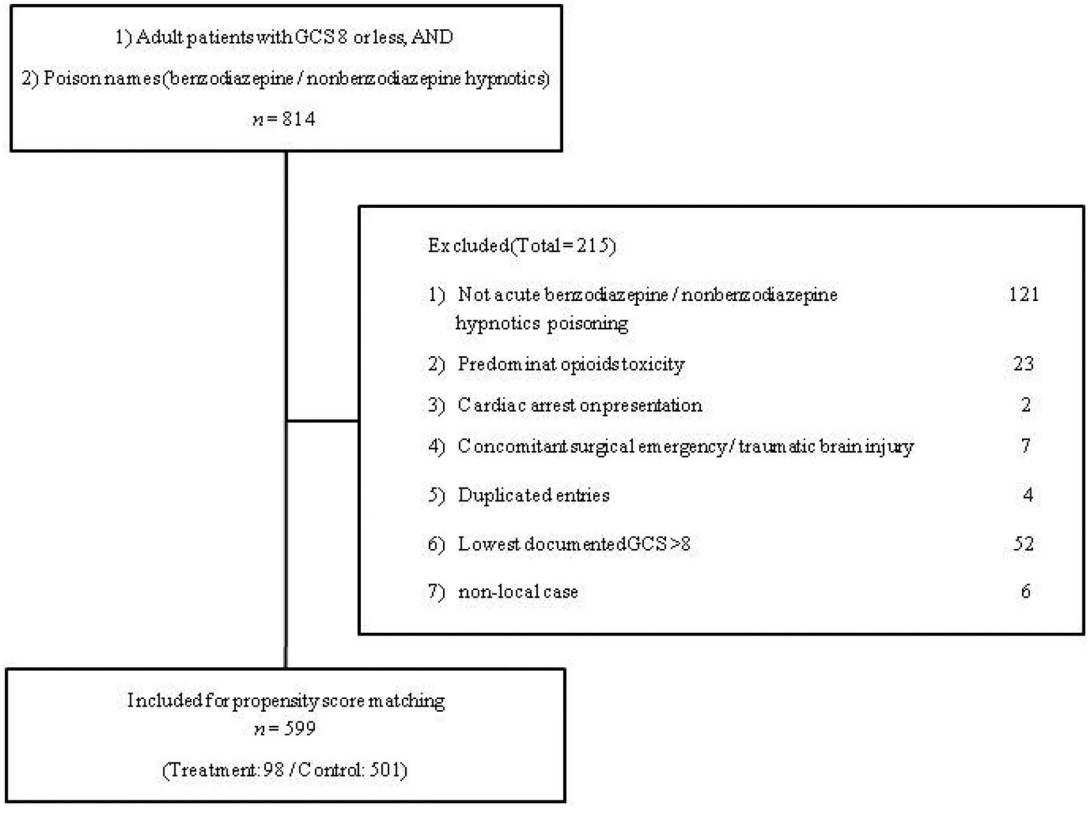

Figure 1. Flow chart of exclusion.

Table 1. Demographic and clinical characteristics of all included patients.

Characteristic	Total $n=599$ (%)	Treatment $n=98$ (%)	Control $n=501$ (%)	*P*-value
Gender				
Female	382 (63.8)	60 (61.2)	322 (64.3)	0.566
Male	217 (36.2)	38 (38.8)	179 (35.7)	
Age, year-median (IQR)	49 (37.5–65)	56.5 (40.25–69)	48 (37–64)	0.081
Benzodiazepines	293 (48.9)	57 (58.2)	236 (47.1)	0.045
Nonbenzodiazepine hypnotics	418 (69.8)	59 (60.2)	359 (71.7)	0.024
Co-ingestion	439 (73.7)	62 (63.3)	377 (75.2)	0.014
Alcohols	100 (16.7)	15 (15.3)	85 (17.0)	0.687
Opioids	36 (6.0)	3 (3.1)	33 (6.6)	0.245
Neuroleptics	154 (25.7)	17 (17.3)	137 (27.3)	0.038
Tricyclic antidepressants (TCA)	50 (8.3)	4 (4.1)	46 (9.2)	0.111
Antidepressants (non-TCA)	176 (29.4)	20 (20.4)	156 (31.1)	0.033
Antiepileptics	62 (10.4)	10 (10.2)	52 (10.4)	0.958
Antihypertensives	44 (7.3)	5 (5.1)	39 (7.8)	0.352
Clinical presentation				
GCS, median (IQR)	5 (3–7)	5 (3–7)	6 (3–7)	0.231
GCS 3–5	300 (50.1)	55 (56.1)	245 (48.9)	0.191
GCS 6–8	299 (49.9)	43 (43.9)	256 (51.1)	
Respiratory failure	117(19.5)	22(22.4)	95(19.0)	0.426
Hypotension	147(24.5)	17(17.3)	130(25.9)	0.07
Tachycardia	197(32.9)	17(17.3)	180(35.9)	<0.001
Bradycardia	27(4.5)	4(4.1)	23(4.6)	1.000
Vomiting	61(10.2)	6(6.1)	55(11.0)	0.146
Seizure	15(2.5)	2(2.0)	13(2.6)	1.000
ECG				
QRS ≥100 ms	145(24.2)	18(18.4)	127(25.3)	0.140
QRS ≥120 ms	49(8.2)	6(6.1)	43(8.6)	0.416
QTc ≥460 ms	151(25.2)	22(22.4)	129(25.7)	0.491
QTc ≥480 ms	85(14.2)	12(12.2)	73(14.6)	0.546
QTc ≥500 ms	36(6.0)	5(5.1)	31(6.2)	0.679

Abbreviations: GCS, Glasgow Coma Score; IQR, interquartile range; QRS, QRS interval; QTc, corrected QT interval.

Table 2. Demographic and clinical characteristics of matched cohort.

Characteristic	Treatment $n=98$ (%)	Control $n=98$ (%)	*P*-value
Gender			
Female	60 (61.2)	56 (57.1)	0.561
Male	38 (38.8)	42 (42.9)	
Age, year-median (IQR)	56.5 (40.25–69)	50.5 (40.25–68)	0.391
Benzodiazepines	57 (58.2)	57 (58.2)	1.000
Nonbenzodiazepine hypnotics	59 (60.2)	62 (63.3)	0.659
Co-ingestion	62 (63.3)	61 (62.2)	0.883
Alcohols	15 (15.3)	14 (14.3)	0.841
Opioids	3 (3.1)	4 (4.1)	1.000
Neuroleptics	17 (17.3)	15 (15.3)	0.699
Tricyclic antidepressants (TCA)	4 (4.1)	2 (2.0)	0.683
Antidepressants (non-TCA)	20 (20.4)	22 (22.4)	0.728
Antiepileptics	10 (10.2)	10 (10.2)	1.000
Antihypertensives	5 (5.1)	5 (5.1)	1.000
Clinical presentation			
GCS, mean (SD)	4.97 ± 1.93	5.12 ± 2.05	0.591
Respiratory failure	22(22.4)	27 (27.6)	0.409
Hypotension	17(17.3)	15 (15.3)	0.699
Tachycardia	17(17.3)	18 (18.4)	0.852
Bradycardia	4(4.1)	3 (3.1)	1.000
Vomiting	6(6.1)	7 (7.1)	0.774
Seizure	2(2.0)	2 (2.0)	1.000
ECG			
QRS ≥100 ms	18(18.4)	19 (19.4)	0.855
QRS ≥120 ms	6(6.1)	7 (7.1)	0.774
QTc ≥460 ms	22(22.4)	21 (21.4)	0.863
QTc ≥480 ms	12(12 .2)	10 (10.2)	0.651
QTc ≥500 ms	5(5.1)	5 (5.1)	1.000

Abbreviations: GCS, Glasgow Coma Score; IQR, interquartile range; QRS, QRS interval; QTc, corrected QT interval; SD, standard deviation.

Table 3. Summary of flumazenil treatments.

	n (%)	Bolus dose, mg–median (IQR)
Overall patients	98 (100)	0.4 (0.2–0.5)
Full responder	51 (52.0)	0.4 (0.2–0.5)
Infusion	7 (7.1)	0.1–0.5 mg/hr, (13–42 h)
Partial responder	14 (14.3)	0.5 (0.4–0.5)
Non-responder	24 (24.5)	0.5 (0.3–1)

Partial responder: documented clinical improvement but not full normalization of GCS by attending clinicians.

Table 3. Flumazenil bolus was given in the ED in 53 cases (54.8%). Normalization of GCS was observed in 51 cases (52%) while 14 cases (14.3%) showed partial response after the intervention. The median bolus dose of flumazenil used with or without achieving clinical response was 0.4 mg (IQR 0.2–0.5 mg). Flumazenil infusion was used after bolus doses in seven (7.1%) patients.

Figure 2 presents the distribution of wins, losses and ties in the primary outcome. In the intervention group, the proportion of wins was 59.8%, while the proportion of losses was 35.6%. The majority of wins were attributed to reduction in ICU admission (64.2% of total wins). The intervention group had a significantly improved primary outcome compared with the control group, with a win ratio of 1.68 (95% CI 1.17–2.41; $P=0.005$). The proportion of ties was 446 (4.6%), giving a win odds of 1.64 (95% CI 1.16–2.31; $P=0.005$). The number needed to treat (NNT), which was

Figure 2. Distribution of wins, ties, and losses for patients.

Table 4. Primary outcome.

	Result (95% CI)	*P* value
Win ratio	1.68 (1.17–2.41)	0.005
Net benefit	0.24 (0.07–0.41)	0.006
Win odds	1.64 (1.16–2.31)	0.005

Win ratio: overall wins/overall losses.
Net benefit: (overall wins − overall losses)/(overall wins + losses + ties).
Win odds: (half of overall ties + overall wins)/(half of overall ties + overall losses).

Table 5. Secondary outcomes.

Outcome	Treatment *n* = 98	Control *n* = 98	*P*-value
Death (%)	2 (2.0)	1 (1.0)	1.000
ICU admission (%)	42 (42.9)	68 (69.4)	<0.001
LOS, median (IQR)	4 (2 − 7.75)	5 (3–8)	0.317
Mechanical ventilation (%)	35 (35.7)	64 (65.3)	<0.001
Pneumonia (%)	30 (30.6)	27 (27.6)	0.753

Abbreviations: ICU, intensive care unit; IQR, interquartile range; LOS, length of hospital stay.

estimated from the net benefit (Table 4), for faring better in the primary outcome was five (95% CI 3–15).

The results of secondary outcome are shown in Table 5. Among the primary outcome components, the intervention group had a significantly lower ICU admission rate than the control group (42.9% vs 69.4%, $P < 0.001$). The proportion of patients who received mechanical ventilation was also significantly less in the intervention group (35.7% vs 65.3%, $P < 0.001$). An exploratory analysis between the patients receiving and not receiving intubation showed intervention response was associated with reduction in intubation (full responder: odds ratio 5.8, 95% CI 2.3–14.5; partial responder: odds ratio 6.4, 95% CI 2.5–16.1). There were three death cases in the matched cohort. Mortality relatedness with the ingested poisons was ruled possible and definite for the two cases in the intervention group. The death in the control group was ruled probable by HKPCC. No significant difference was found between the two groups in the number of deaths, median length of hospital stay and incidence of rapid-onset pneumonia.

Concerning the major adverse events in the intervention group, two patients developed seizures after admission with one death. One patient developed torsades de pointes and survived. The seizure rate in the intervention group was similar to that in the overall study population (2% versus 2.5%). Clinical details of the four cases with major adverse events were reported in Supplementary Table 4. Case one was a 36-year-old who overdosed zopiclone with cough mixture co-ingestion. The patient developed a seizure shortly after flumazenil treatment, which aborted spontaneously within a minute. After resolution of toxicity from overdose, the patient was discharged from the ICU on day three. Five days post overdose and 24-hours post ICU discharge the patient suffered a cardiac arrest and could not be resuscitated. The seizure was likely attributed to flumazenil based on the strong temporal relationship and history of hypnotic dependence. On the other hand, the death was deemed unrelated to flumazenil judging from the timeline of clinical deterioration. For case two, no vomiting, agitation or seizure occurred after the administration of flumazenil. The patient developed aspiration, respiratory failure and septic shock

after sole zopiclone overdose, eventually succumbed on day two admission. In case three, the temporal relationship between intervention and seizure was unclear. Case four had mixed donepezil and clonazepam overdose with progressive QT interval prolongation to above 500 ms. The patient's rhythm evolved to torsade de pointes several hours after the last dose of flumazenil. Based on the weak temporality, and known QT interval prolongation and torsade de pointes associated with donepezil [28,29], the dysrhythmia was unlikely to be attributed to flumazenil.

Discussion

The controversy surrounding the use of flumazenil treatment in patients with acute poisoning originated from its uncertain risk-benefit profile. Despite its proven efficacy in rapidly improving GCS among those solely intoxicated with benzodiazepine and nonbenzodiazepine hypnotics [30], flumazenil failed to outperform the control in most clinical benefit parameters previously being studied, including the number of costly or complex procedures, ICU admission rate, length of ED/ICU/hospital stay and costs [21,22,31]. The complex nature of overdose ingestion and the small number of patients in the intervention group were the common obstacles to quantifying the benefit of flumazenil. Razavizadeh et al. [31] reported that flumazenil infusion could reduce mechanical ventilation in patients with severe sole benzodiazepines poisoning. Our study attempted to construct a balanced cohort with co-ingestion, ECG, and clinical features of acute toxicity by propensity score matching. Hierarchical composite endpoint was selected to increase the statistical power in a small sample size study.

Our study showed that intervention group had a 68% greater likelihood of winning in the hierarchical composite endpoint. As the wins for in-hospital deaths and length of hospital stay were both outnumbered by losses, the observed difference was predominantly attributed to the reduction of ICU admission in the intervention group. Barnett et al. [22] reported similar observations regarding the trend of decreased ICU admission rates. It is possible that the decision to admit to the ICU occurred prior to the intervention in some cases in our study. However, such confounder would bias the results toward a diminished benefit, and our conclusion would still be true. In our study, the reduction in ICU admission was closely related to the reduction in mechanical ventilation (odds ratio 32.2, 95% CI 14.3–72.6). The significant difference in rate of intubation between groups of intervention responder (full 17.6% vs partial 35.7% vs non-responder 79.2%) suggested intervention response contributing to the winning in primary outcome.

Because of the study design, the indications of endotracheal intubation and mechanical ventilation could not be evaluated in every case. Undoubtedly, intubation was performed as a preventive measure for aspiration in some of the cases [32]. Such practice might change with the emerging evidence on benefit of conservative strategy of withholding intubation in acute poisoning [33,34]. Freund et al. reported significant benefit of noninvasive airway management strategy in their randomized controlled trial with reduction in mechanical ventilation, ICU length of stay, ICU admission rate as well as adverse event from intubation [34]. However, patients with unstable respiratory status were excluded from the above trial. As one-fourth of our patients presented with respiratory failure, the effect size of flumazenil treatment would be decreased but unlikely to be completely offset by the strategy of withholding intubation.

In our study, the findings on length of hospital stay and incidence of rapid-onset pneumonia are concordant with Mathieu et al. [21] and Razavizadeh et al. [31] previously reported. While flumazenil antagonizes benzodiazepines and nonbenzodiazepine hypnotics in the central nervous system (CNS), it does not enhance the elimination of poisons from the body. With a shorter duration of action and half-life than most benzodiazepines and nonbenzodiazepine hypnotics, resedation after awakening was commonly observed after bolus administration in more than half of the patients [22,35]. In contrast to heroin (diacetylmorphine) overdose revived with naloxone that could be safely discharged [36], close surveillance cannot be omitted after flumazenil bolus with or without infusion. Aspiration could occur at any occasions throughout the course of intoxication. Although aspiration during intubation might be reduced with the decrease in mechanical ventilation after flumazenil, it could still occur prior to admission, during resedation, or under effect from co-ingestions resulting in pneumonia [37].

Weighting the estimated NNT against the low occurrence of major adverse events, flumazenil treatment shows potential for improving resource utilization. An average of five patients treated with flumazenil would result in one better outcome, most probably being one less ICU admission. Moreover, adverse events from intubation (e.g., hypoxemia, hypotension, oesophageal intubation dental injury) could also be reduced with a decrease in mechanical ventilation [30]. After the adoption of non-invasive airway management in comatose patients with acute poisoning, future studies on flumazenil treatment should be conducted to evaluate the

consistency of benefit. Nevertheless, the benefit could hardly be considered as lifesaving. While supportive treatment is of paramount importance in patient management and should never be surpassed by a non-life saving antidote; flumazenil treatment could be beneficial in good hands with careful patient selection and cautious dosing.

Limitations

This study has several limitations. First, the retrospective nature of the study limited the data we can extract. Clinical features such as mental status are subjectively determined by the attending clinicians. Information bias and missing data are unavoidably present. Second, unlike a randomized controlled trial, propensity score matching could only account for measured covariates; results might be biased from those unmeasured factors including clinician decision-making and changes in practice over time. Third, the administration of flumazenil was inconsistent and varied between clinicians and clinical areas (ED, ICU, wards). Fourth, patient selection, pattern of co-ingestion and availability of supportive measures can change significantly throughout the study period (16 years) and increased patient heterogeneity. Lastly, not all patients had laboratory confirmation of poison exposure, approximately 12% of cases relied on history.

Conclusion

This study suggests that flumazenil treatment was associated with reduction in ICU admission and need for mechanical ventilation; as well as a better outcome with regard to the composite endpoint of in-hospital death, ICU admission rate, and length of hospital stay among comatose patients with acute benzodiazepines or nonbenzodiazepine hypnotics poisoning.

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Data availability statement

Raw data were generated at Hong Kong Poison Control Centre. Derived data supporting the findings of this study are available from the corresponding author, upon reasonable request.

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