Abstract

Background
There are no published reports in Canada examining paramedic use of ketamine for highly agitated patients or excited delirium syndrome. We employed a Plan, Do, Study, Act (PDSA) quality improvement approach to evaluate the safety and effectiveness of advanced care paramedic administered intramuscular (IM) ketamine for patients with extreme agitation in the out-of-hospital setting.

Methods
Data were prospectively collected from July 2018 to January 2019 when advanced care paramedics with specific training administered IM ketamine as an alternative to midazolam. Paramedics used a clinical audit form to document the ketamine dose, patient response on the Richmond Agitation Sedation Scale (RASS) at time intervals, adverse effects, and any airway management interventions they performed.

Results
Thirty-three patients received either 4 mg/kg or 5 mg/kg of ketamine. Combining data for both doses, the median change in RASS score at 5 minutes post-ketamine was 3 (range 0 to 8) and statistically significant for each dose. There were seven cases (21%) with reported adverse effects including SpO2 <90% (3/7), hypersalivation (3/7), trismus or teeth grinding (2/7), muscular rigidity (1/7) and laryngospasm (1/7). Statistical analysis confirmed that the incidence of adverse events was not dose dependent. Basic airway management was performed in one-third of all cases.

Conclusion
We piloted the implementation of ketamine for sedation in our paramedic system by employing a PDSA cycle. Ketamine 5 mg/kg IM provided effective control of acutely agitated patients with adequate sedation at 5 minutes post-delivery. Any adverse events that occurred as a result of IM ketamine were readily managed with basic airway management interventions.

Keywords:
ketamine; sedation; paramedic; PDSA; agitation; excited delirium; emergency medical services

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Introduction

Paramedics are routinely called to manage highly agitated and combative patients. A subset of these patients are suffering from excited delirium syndrome (ExDS), an acute behavioural disorder coupled with metabolic disturbances that may be fatal if not treated in a timely manner (1). Though the pathway to death in ExDS is unknown, experts suggest it will progress if left untreated, causing a combination of acidosis, sympathomimetic surge and hyperthermia. The estimated mortality rate for ExDS ranges from 8.3% to 16.5% (2-5). Patients experiencing ExDS are more likely to have an underlying mental health condition and to use illicit drugs (5). Ultimately, they present as a danger to themselves as well as to paramedics and other emergency responders.

Paramedics are now using ketamine, a dissociative anaesthetic, for the purpose of sedation. As an alternate strategy, a subset of BCEHS paramedics can employ sedation as a pharmacological intervention. Advanced Care Paramedics (ACPs) in our system have traditionally administered a benzodiazepine when standard de-escalation proves ineffective. Our clinical practice guideline for managing highly agitated patients includes midazolam 5–10 mg via intramuscular (IM) injection with an option to repeat the dose once if needed (8). IM midazolam has drawbacks when patients require rapid and safe sedation (9) including an onset time of 15–20 minutes and an associated risk of cardiorespiratory compromise (10). To manage extreme agitation in the emergency department, physicians are more likely to use benzodiazepines as an adjunct to antipsychotics such as haloperidol or droperidol (11-14). Recently, ketamine has been introduced to the out-of-hospital setting as a feasible alternative for this purpose (8).

Methods

Study design and setting
We performed this quality improvement study by using a PDSA cycle. Speroff and O’Connor describe how a four-step PDSA project aims to determine whether a suggested change is actually an improvement.

1. Plan – predict what will happen and plan for data collection.
2. Do – carry out the plan using a study protocol and collect the data.
3. Study – analyse, interpret and summarise the results.
4. Act – determine any changes required and implement the improvement initiative (29).

Serving a provincial population of 4,810,000, BCEHS responds to more than 750,000 calls annually (30). Of these events in 2018, approximately 3400 patients were identified as potentially experiencing severe agitation; and 120 agitated patients were pharmacologically sedated with IM midazolam. The option to give sedation is limited to our 360 advanced and critical care paramedics who account for approximately 12% of our paramedic workforce. The majority of severely agitated patients are treated and transported solely by primary care paramedics who are not licensed to administer sedation.

In 2018, our paramedic service decided to trial whether the paramedics could use ketamine as an alternative to midazolam...
for sedation. This was in response to ACPs documenting concerns over an increased incidence of encounters with agitated patients and their perception that midazolam was an inadequate sedative. ACPs use the RASS to measure and document patient sedation. They reported that patients were requiring repeated doses of midazolam to achieve a low enough RASS score for safe transport, posing an increased risk to patient and practitioner safety.

The RASS is a validated observational instrument used to assess levels of patient sedation and agitation. It uses a 10-point scale (+4 to -5) with discrete criteria for levels of sedation and agitation (31). Using the RASS tool, we aimed to measure the effectiveness of advanced care paramedic administered IM ketamine to reduce patient agitation. Consistent with our clinical practice guidelines, we assessed the effectiveness of sedation by comparing the patients’ original RASS score against a target of +2 to -2 at 5 minutes after drug administration. We selected a 5-minute interval as a practical timeframe for paramedics to rapidly gain control of volatile situations. We also asked paramedics to report their levels of satisfaction as an additional endpoint for effectiveness. To measure the second objective of patient safety, ACPs documented adverse effects that occurred post ketamine administration and anytime they performed basic or advanced airway management procedures.

Based on a review of contemporary literature and emergency physician expert advice, our prediction was that a single dose of 4 mg/kg IM ketamine would be a viable alternative to midazolam and achieve adequate sedation levels without compromising patient safety (15,16). Our PDSA project plan involved allowing a select group of ACPs in two major metro centres to use ketamine as a first line sedative for patients with extreme agitation. In total, 36 paramedics from two centrally located ambulance stations were trained and eligible to take part in the project.

The ACPs received approximately 2 hours of education on the pathophysiology and accurate recognition of severe agitation and ExDS as well as the pharmacodynamics and administration of ketamine. We also provided a refresher on the use of RASS (Table 1). The ACPs completed an online learning module followed by an in-person session led by the primary investigators. Paramedics were required to pass an on-line knowledge assessment and successfully complete a case simulation during the face-to-face session. The paramedics concurrently completed a two-day Advanced Airway Interventions and Management in Emergencies (AIME) course before being able to administer ketamine (32). In addition, all receiving hospitals were notified of the new protocol.

Consistent with our organisation’s policy, we assessed the project using our ethics guidelines screening tool. As a quality assurance study that was used for standard program activities, our project was deemed to have minimal risk implications and was exempt from institutional board review.

Table 1. The Richmond Agitation Sedation Scale

| Score | Term          | Description                                                                 |
|-------|---------------|------------------------------------------------------------------------------|
| +4    | Combative     | Overtly combative or violent; immediate danger to staff                       |
| +3    | Very agitation| Pulls on or removes tube(s) or catheter(s) or has aggressive behaviour toward staff |
| +2    | Agitated      | Frequent non-purposeful movement or patient-ventilator dyssynchrony           |
| +1    | Restless      | Anxious or apprehensive but movements not aggressive or vigorous              |
| 0     | Alert and calm| Adequate sedation for transport                                                |
| -1    | Drowsy        | Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice |
| -2    | Light sedation| Briefly (less than 10 seconds) awakens with eye contact to voice              |
| -3    | Moderate sedation | Any movement (but no eye contact) to voice                                   |
| -4    | Deep sedation | No response to voice, but any movement to physical stimulation               |
| -5    | Unarousable   | No response to voice or physical stimulation                                   |

Source: Sessler CN, Gosnell M, Grap MJ, et al (2002)

Participants

Patients meeting inclusion criteria were defined as having severe agitation and combativeness consistent with acute behavioural disturbance due to potential ExDS with a RASS score of +4 (combative) to +3 (very agitated) who could not be safely conveyed to the hospital without pharmacological intervention. Patients of all ages who fit this criterion and were given ketamine by a study-trained paramedic between July 2018 and January 2019 were included in the study. Patients who required sedation for RASS scores less than +3 received midazolam per the standard treatment guidelines and were not included in the project.

Protocol

The following project protocol describes the actions representing ‘do’ in our PDSA cycle. All patients who met the inclusion criteria initially received 4 mg/kg IM ketamine. In the first 3 months of the study, paramedics signalled a safety concern by submitting incident reports of insufficient patient sedation. The clinical governance committee reviewed these incidents and in October 2018 we subsequently decided to increase the ketamine dose to 5 mg/kg which is the upper limit reported in published literature (4,17).
Paramedics estimated the patient’s weight in most cases. Using a purpose-built electronic clinical audit form, the ACPs documented each time they gave ketamine for extreme agitation and signs of ExDS. The completed form was submitted directly to a primary investigator. This triggered an alert to the medical director who then contacted each paramedic crew by telephone as soon as possible to discuss the case, especially if any adverse effects were observed.

In addition to the patient’s age and gender, the pre- and post-ketamine RASS were recorded at time 0, 5 and 10 minutes and on arrival to the emergency department. Paramedic perception of sedation effectiveness was measured using a Likert scale of 1 (no effect) to 5 (very effective). They also documented the total time to adequate sedation as a record of ‘administration-to-sedation duration’ in minutes. Using a drop-down menu, paramedics recorded the use of airway adjuncts including jaw thrust, nasopharyngeal airway, oropharyngeal airway, supraglottic airway and endotracheal intubation, as well any adverse effects including vomiting, SpO₂ <90%, hypersecretions requiring suctioning, trismus, muscle rigidity and laryngospasm. Appreciating that the aforementioned adverse effects may also be symptoms associated with the patient’s primary complaint, we advised paramedics to use their best judgement to determine if they occurred as a result of ketamine administration. Paramedics rated the adequacy of the duration of sedation and the suitability of training materials using binary yes or no responses on the data collection form and had a free text form for additional comments. We were able to document the initial dispatch assigned event code for each case. Paramedics also recorded standard observations such as the patient’s Glasgow Coma Score, temperature, blood pressure and heart rate on the patient care record but these are not reported as part of this project.

Data analysis

Representing the ‘study’ step in our PDSA cycle, our data analysis and results are presented next. The data were collected using an electronic form and manually collated in an Excel™ spreadsheet (Microsoft Corporation). Frequencies and descriptive statistics were analysed using IBM SPSS Version 25. To answer the question of effectiveness, our primary outcome was a change in RASS scores to a target range between +2 and -2 at 5 minutes after ketamine administration. In addition, we used paramedic reports of time to adequate sedation and their perceptions of effectiveness as secondary measures. Outcomes related to the safety of ketamine administration included quantifying the type and frequency of adverse effects observed as well as type and frequency of airway adjuncts that paramedics used.

Results

Sample characteristics
A total of 34 patients received ketamine sedation for extreme agitation during the project period. One patient was excluded when it was determined that the patient had a traumatic brain injury rather than an acute behavioural disturbance. Analysis of aggregate data reveals that of the 33 remaining patients included in the project, 61% were male with an average age of 30 years. Within the study population, 19/33 (58%) patients were identified as having ingested illicit drugs including one or more of cocaine, lysergic acid diethylamide, methamphetamine, heroin, marijuana, ketamine and opioids. This was documented as ‘none’ for one patient and ‘unknown’ in 13 cases. The characteristics of the patients who received ketamine are summarised in Table 2. The primary dispatch assigned event codes were for psychiatric/abnormal behaviour (42%) and overdose/poisoning (18%). The additional codes are presented in Table 3.

Table 2. Characteristics of cases with patients who received ketamine (n=33)

| Characteristic                                      | Value  |
|-----------------------------------------------------|--------|
| Age: mean (SD), (range 17–56 years)                 | 30.4 (11.2) |
| Gender: male, %                                     | 61%    |
| Dispatch code: psychiatric/abnormal behaviour, %    | 42%    |
| Accompanying intoxicant documented: %               | 58%    |

Table 3. Dispatch-assigned event codes

| Dispatch code                          | # Cases |
|----------------------------------------|---------|
| psychiatric/abnormal behaviour         | 14      |
| overdose/poisoning                     | 6       |
| unconscious                            | 2       |
| assault                                | 2       |
| sick person                            | 2       |
| seizure                                | 2       |
| burns                                  | 1       |
| animal bite                            | 1       |
| heart problem                          | 1       |
| interfacility transfer                 | 1       |
| haemorrhage                            | 1       |

Ketamine administration and time to adequate sedation
Throughout the project, 42% (n=14) received 4 mg/kg of IM ketamine and 58% (n=19) received 5 mg/kg. The mean IM total dose of ketamine was 379 mg (range 150–600 mg, SD 113 mg); 10 cases did not have the time to adequate sedation entered. In 23/33 of complete records, the time to adequate sedation was reported as a mean of 4.7 minutes (range 0.5–13 minutes, SD 3.5 minutes).

RASS scores and reported effects
All patients entered in the study had an initial RASS of either +4 (n=20) or +3 (n=13). We are reporting the median scores as RASS score data were unevenly distributed.
Though it was not part of the original study protocol, we are also reporting our RASS findings based on the administered dose (Table 4).

Mann-Whitney testing on the RASS score at 5 minutes (median 0, range 0-8) revealed an equivalent reduction for patients with an initial RASS of +4 or +3 (p=0.102). When combining data on both doses, the overall median change in RASS score at 5 minutes post-ketamine administration was 3 (range 0 to 8). The change in RASS at 5 minutes was determined to be statistically significant for all patients who received 4 mg (p=0.0002) or 5 mg (p<0.0001) (Figure 1). When comparing doses however; our data did not demonstrate a statistically significant difference in the change in RASS at 5 minutes post-ketamine (p=0.494).

Of interest is that 57% (8/14) of patients who received 4 mg/kg had a change in RASS score of <4 after 5 minutes and that on arrival to the emergency department, 45% (n=13) of all patients had a recorded RASS score of -4 (deep sedation) or -5 (unarousable).

The paramedics reported that ‘effective’ or ‘very effective’ sedation was achieved in 82% (27/33) of patients. In the four cases in which paramedics reported dissatisfaction with the sedation, the patients remained with a RASS of +3 at 10 minutes post-ketamine administration. Three of these patients had been given 5 mg/kg of IM ketamine and had reportedly used one or more of methamphetamines, ketamine, heroin or other opioids.

### Adverse effects and airway interventions

Focussing on the primary endpoint to measure patient safety, there were seven cases (21%) with reported adverse effects including SpO2 <90% (3/7), hypersalivation (3/7), trismus or teeth grinding (2/7), muscular rigidity (1/7) and laryngospasm (1/7) (Table 5). In the one reported incidence of laryngospasm, the paramedics discussed the case with the medical director and concluded that this was the most likely cause of the patient’s presentation. It was managed with short-term bag valve mask ventilation. Though the majority (n=5) of cases with recorded adverse events occurred at the higher dosage range of 5 mg/kg, statistical analysis confirmed that the incidence of adverse events was not dose dependent (p=0.67, Fishers exact test).

Airway management data revealed that 11/33 (33%) patients received some form of basic airway management and none required a supraglottic airway or endotracheal intubation. 14% (2/14) of patients who received 4 mg/kg of ketamine

| Dose  | n   | Initial RASS | 5 minutes | 10 minutes | ED arrival |
|-------|-----|--------------|-----------|------------|------------|
| 4 mg/kg | 14  | +4 (range +4 to +3) | +1 (range +3 to –3) | -2 (range +3 to –4) | -2 (range +3 to –4) |
| 5 mg/kg | 19  | +4 (range +4 to +3) | 0 (range +4 to –4) | -3 (range +3 to –5) | -4 (range +4 to –5) |

![Figure 1. Ranked change in RASS scores at 5 minutes by dose](image)
required placement of either an oropharyngeal airway (OPA) or nasopharyngeal airway (NPA), while 47% (9/19) who received 5 mg/kg required either a jaw thrust (1/19), basic airway adjunct in the form of an OPA or NPA (7/19) or ventilatory support with a bag valve mask (BVM) (1/19). In eight cases, paramedics performed a basic airway intervention but did not report an adverse event. When comparing the two doses of ketamine, the differences in airway management was not found to be statistically significant (p=0.067, Fishers exact test).

Discussion

Our aim was to determine the safety and effectiveness of paramedic administered IM ketamine for highly agitated patients in the out-of-hospital setting. As part of the ‘act’ step in our PDSA project, we offer the following discussion points for consideration. With respect to effectiveness, our paramedics reported that they were satisfied that ketamine achieved favourable results in the majority of situations. We quantified this with RASS scores describing most patients presenting as either ‘restless’ or ‘alert/calm’ 5 minutes after ketamine was given. Of the 23/33 cases where it was recorded, our findings demonstrate that effective sedation occurred in a mean of 4.7 minutes. This is consistent with Cole et al who found that ketamine was effective in 5 minutes as compared to haloperidol in 17 minutes (2). Similarly, Riddell et al found ketamine to have a faster onset than benzodiazepines in their study of 98 emergency department patients (11). In their systematic review of ketamine in the emergency department and out-of-hospital settings, Mankowitz et al report an average 7.2 minutes to adequate sedation (23) while Scheppke et al achieved effective sedation and medical control in just over 2 minutes (16). Overall the research shows varied results when looking at time to adequate sedation as a measure of effectiveness.

During the course of our project we used a dose of 4–5 mg/kg which is within the parameters of high dose ketamine for sedation described in pre-hospital literature. Horton and Scheppke et al each used 4 mg/kg in their respective studies of 52 patients while Olives et al reports using 5 mg/kg in a study involving 135 cases (15-17). Similarly, seven patients in a study by Scaggs et al were also given 5 mg/kg (4). Our paramedics determined the lower dose to be inadequate despite no statistically significant difference in the change of a patient’s RASS score at 5 minutes when comparing doses.

The mean ketamine dose of 379 mg we recorded is higher than the 324 mg reported by Keseg et al and Mankowitz et al whose review of 650 patients across 18 pre-hospital and emergency studies revealed an average IM dose of 315 mg (23,28). Of interest is that we did not specify a maximum dose in our study. In their literature review of pre-hospital ketamine for ExDS and agitation, Linder et al also noted that paramedics did not typically have a maximum dose and recommends that one should be set (19).

Our paramedics also recorded an estimated weight on only 60% of patients which is comparable to a study by Hollis where paramedics recorded weights on 26/38 patients (25). Research on paramedic weight estimation is mixed (33-35) and we are unable to confirm whether the ACPs estimated weights with any degree of accuracy, something that would affect the dose of ketamine given, and would require further study.

We reviewed our findings on the effectiveness of ketamine in the context of Campeau’s Space-Control Theory of Paramedic Scene Management that highlights how hazardous and complex the out-of-hospital environment can be. Campeau emphasises the important role that paramedics have in bringing order to chaotic scenes and how they have to find a balance between providing care while ensuring safety for both the patient and practitioners (6). In this project, we used the RASS as a quantitative measure to evaluate how effective ketamine is when given for extreme agitation – that is, did it achieve the desired result? While our findings demonstrate that RASS scores will decrease with ketamine, they are unable to quantify other more complex aspects of effectiveness. We recognise that these findings must be interpreted within a broader context and that effectiveness, in the opinion of a paramedic at the scene, extends beyond a RASS score. For example, a patient with a high potential for a communicable disease that has been spitting at emergency responders may still pose a potential threat despite a reduced RASS score. In addition, the number and type of resources at a scene who can assist during the transport of a patient with a known history of violence may impact whether a paramedic feels that a patient is adequately sedated.

In our experience, most patients with acute behavioural disorder showed a significant reduction in agitation with ketamine, thus reducing the risk of ExDS and its potential sequelae. We also
examined patient safety by measuring adverse effects attributed to ketamine, especially those that required subsequent airway management. Our findings include adverse effects reported in 7/33 cases (21%) including SpO2 <90% (9%), hypersalivation (9%), trismus (7%), muscle rigidity (3%) and laryngospasm (3%). This experience with ketamine differs from Mankowitz et al who found a documented average hypoxia rate of 1.8% and 18.8% hypersalivation post-ketamine. They do report a comparable rate of laryngospasm at 1.3% (23). Notably, Cole et al report hypersalivation in 38% of cases and laryngospasm in 5% of patients (n=64) (2). We are unable to explain the low incidence of observed hypersalivation in our patient population. Though not included in our project, the research also identifies emergence reactions as a commonly reported adverse effect of ketamine (19,23,36).

To manage adverse effects, 30% (10/33) of our patients received basic airway management in the form of a jaw thrust, placement of an airway adjunct (OPA or NPA) and, in one case, bag-valve mask ventilation. In our experience, the majority of adverse events and subsequent airway interventions occurred with the higher dose of 5 mg/kg, though this was not a statistically significant finding. Follow-up telephone calls by the medical director to the paramedics did not reveal any additional concerns beyond those reported on the audit forms.

It is noteworthy that none of the patients in our project required an advanced airway in the out-of-hospital environment. This contradicts a recurring theme in the ketamine literature that associates its use in agitiation with high rates of intubation. Examples of intubation rates for agitated patients receiving pre-hospital ketamine are reported by American researchers Olives et al (17) at 63% (85/135), Cole et al (2) at 39% (25/64), and by Keseg et al (28) at 22% (8/35). As we did not follow our patients beyond the pre-hospital setting, we are unable to report on the incidence of intubation in the emergency department. Given that none of our ACPs elected to intubate, which is within their scope of practice, we interpret this as a surrogate finding that our patients did not require advanced airway management. This may be due to the paramedic comfort level with patients who are sedated yet stable and still maintaining their airway with minimal intervention. Olives et al suggest that the high rates of intubation in their study may be due to a lack of provider comfort when dealing with sedated patients post-ketamine administration (17). This explanation is further supported by Cole et al who suggest in a follow-up report that some of the intubations reported in earlier studies may have been avoidable and involved practitioners misapplying the GCS axiom ‘GCS less than 8, intubate’ (1). Cole recently coined the term ‘GCS-3K’ to explain the phenomenon that although patients given high doses of ketamine are a GCS-3, it is due to the ketamine alone and deliberate dissociative anaesthesia. These patients are not obtunded as a result of shock, respiratory failure, metabolic derangement or head injury and therefore the conventional teaching around airway management may be misleading (2).

PDSA outcome
Following the PDSA methodology of this quality improvement project, we proceeded to ‘act’ on our findings. Our experience enabled us to implement ketamine for use by all ACPs in our paramedic system to manage severe agitation and potential ExDS. On reviewing the data, we updated the clinical practice guidelines for ACPs in October 2019 to include ketamine 5 mg/kg IM as a first line option for severe agitation (RASS +4 to +3). We recognise that approximately 33% of patients who receive high dose ketamine may require some form of airway intervention. For this reason, all ACPs will continue to receive initial ketamine training in conjunction with the AIME course. During AIME they are taught a staged approach to airway management including basic, intermediate and advanced airway skills to ensure they have the knowledge, skills and ability to anticipate and manage any airway compromise or adverse effects following the administration of ketamine.

In summary, after studying its effectiveness and safety using a PDSA cycle, ketamine 5 mg/kg IM has now been implemented for ACP use for undifferentiated patients experiencing extreme agitation and potential ExDS. We continue to monitor this strategy through our regular quality improvement audits. The lessons learnt through this project also include the importance of comprehensive data collection and analysis for new clinical initiatives as well as the need for paramedics to provide high-quality patient documentation and complete quality improvement surveys to help monitor and advance clinical practice.

Limitations
This project has several important limitations. First, we relied on paramedics to complete the clinical audit form after the patient encounter which may introduce bias into the data collection. Second, we used paramedic-assessed RASS scores, which have been shown to differ from scores calculated in the emergency department (36). We also determined that RASS scores alone may not comprehensively measure sedation in the out-of-hospital setting, and that another objective tool would be useful. Third, this study has a small sample size and the results of this sample cannot be used to generalise a larger patient population. In addition, our study did not extend beyond the pre-hospital setting, so we are unable to report on any additional adverse effects, medical interventions, including in-hospital advanced airway management or patient outcomes. Further research is needed to better understand effectiveness and safety of ketamine when managing highly agitated patients in the unique context of the paramedic environment. While this quality improvement project adds to the body of knowledge, more high-quality research needs to be conducted to assess the role of ketamine for extreme agitation and ExDS in the pre-hospital setting.
Conclusion

By employing a PDSA cycle, we were able to pilot the implementation of ketamine for treatment of acute agitation with sedation in our paramedic system. In our experience, ketamine administered at 5 mg/kg IM provided effective sedation 5 minutes post-delivery to highly agitated and combative patients. Any adverse events that occurred as a result of IM ketamine were readily managed with basic airway management interventions.

Competing interests

The authors declare no competing interests. Each author of this paper has completed the ICMJE conflict of interest statement.

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