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Prevalence and Risk Factors for Iatrogenic Opioid Withdrawal in Medical Critical Care Patients

IMPORTANCE: Opioids are the mainstay of pain management and sedation in critically ill patients, which can lead to the development of physiologic tolerance and dependency. The prevalence of iatrogenic opioid withdrawal syndrome (IWS) is reported as 17–32% in the ICU; however, limited evidence exists for the medical ICU patient population.

OBJECTIVES: To identify the and risk factors for IWS in adult patients admitted to critical care medicine services who received greater than or equal to 24 hours of continuous opioid infusion therapy.

DESIGN, SETTING, AND PARTICIPANTS: A prospective, observational study was conducted in a tertiary care hospital in adult medical ICU patients. Ninety-two patients who received greater than or equal to 24 hours of continuous opioid infusions were included in the study.

MAIN OUTCOMES AND MEASUREMENTS: Patients were assessed daily after opioid infusion discontinuation using the Clinical Opiate Withdrawal Scale (COWS) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) opioid withdrawal criteria for a maximum of 5 days. The primary outcome was the prevalence of IWS of moderate severity or greater using COWS. Secondary outcomes included the prevalence of IWS diagnosis of any severity based on COWS, the prevalence of IWS diagnosis based on a positive DSM-V score, and the identification of potential risk factors for developing IWS of any severity.

RESULTS: Four hundred forty-seven patients received greater than or equal to 24 hours of continuous opioid therapy. Of these, 385 were excluded, leaving 92 patients included in the final analysis. Except for a higher prevalence of psychiatric history in the IWS-positive group, baseline characteristics were similar. Overall, 11 patients (12%) developed IWS of moderate severity or greater, based on COWS. The IWS-positive group also had longer durations of opioid infusions, higher cumulative opioid infusion doses, higher mean daily doses, and higher infusion rates at any given time. The concomitant use of dexmedetomidine (38.3 vs 15.6%, $p = 0.014$) and benzodiazepines (63.8 vs 37.8%, $p = 0.021$) during or after the opioid infusion were significantly higher in the IWS-positive group compared with the IWS-negative group. No significant differences were found between the two groups for scheduled or as needed opioids after cessation of the opioid infusion. Continuous opioid infusions greater than or equal to 72 hours and total daily dose greater than or equal to 1,200 µg were found to be independent predictors for the development of iatrogenic opioid withdrawal via logistic regression.

CONCLUSIONS AND RELEVANCE: Approximately one in every eight patients receiving continuous infusion opioid for greater than 24 hours while mechanically ventilated in the medical ICU will develop IWS of moderate severity or greater; this increases to one in three patients diagnosed with DSM-V criteria or any level of IWS severity. Patients receiving opioid infusions greater than or equal to 72 hours, or a total daily fentanyl dose of greater than or equal to 1,200 µg (~ 50 µg/hr) are at a higher risk for developing IWS and should be monitored as part of clinical practice when opioid infusions are discontinued.

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KEY POINTS

Question: What is the prevalence and risk factors of iatrogenic withdrawal syndrome (IWS) in adult medical ICU patients who received opioid continuous infusions for greater than 24 hours? We anticipate that the prevalence of IWS in the medical ICU patient population may be even higher than the surgical/trauma ICU patient population and that higher doses and longer durations will be risk factors.

Findings: In this clinical investigation, the prevalence of IWS was 12% in medical ICU patients when diagnosed as moderate severity or greater using Clinical Opiate Withdrawal Scale; the prevalence was higher and consistent with other studies in ICU patients when using Diagnostic and Statistical Manual of Mental Disorders V criteria.

Meaning: IWS is a concern in medical ICU patients when patients are weaned from opioid infusions and therefore monitoring for its occurrence should be conducted more frequently.

KEY WORDS: analgesics/opioid, Diagnostic and Statistical Manual of Mental Disorders V, iatrogenic disease, intensive care unit, substance withdrawal syndrome

Analgosedation, first introduced in the 2013 Pain, Agitation, and Delirium (PAD) guidelines, is the concept of using analgesia-based sedation in mechanically ventilated patients (1). The recommendation was developed after identification of unrelieved pain as a contributing source of agitation in most critically ill patients (2). Analgosedation is associated with a decrease in ventilator days and ICU length of stay while improving pain relief (3–5). Additionally, the PAD guidelines identified that use of continuous infusion benzodiazepines in the ICU setting was a major risk factor for the development of ICU delirium. Therefore, analgosedation is recommended as the backbone for most sedation regimens in the ICU (5–7).

Since opioids have become the mainstay of ICU analgosedation, there is concern that prolonged exposure to opioids can lead to development of physiologic tolerance and dependency. Opioids stimulate mu, kappa, and delta receptors in the central nervous system (CNS) leading to down-regulation of available receptors. Abrupt removal of the inhibitory signals provided by opioids may lead to CNS stimulation and subsequent opioid withdrawal (8). Iatrogenic withdrawal syndrome (IWS) is a further classification of opioid withdrawal, which can be experienced by critically ill patients when continuous opioid infusions are stopped or weaned abruptly, especially upon extubation at which time sedation or analgesia is often no longer necessary (9). Opioid withdrawal is characterized by agitation, irritability, tachycardia, fever, sweating, and gastrointestinal disturbance, such as vomiting, nausea, and diarrhea (8). Current Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption guidelines recommend tapering opioids to avoid IWS but provide no specific IWS assessment or opioid weaning strategies (7).

Opioid withdrawal assessment tools have been validated in noncritically ill adults. The Diagnostic and Statistical Manual of Mental Disorders (DSM-V) opioid withdrawal criteria is used for diagnosis based on the presence of three or more withdrawal symptoms (10). Similarly, the Clinical Opiate Withdrawal Scale (COWS) is widely used in outpatient settings because of reproducible results, association with buprenorphine maintenance, and ease of application (11). COWS is the summed score of eleven items to assess the stage or severity of opioid withdrawal. The signs and symptoms contribute to the scoring only if they are not attributable to other existing medical conditions. The severity is classified into mild, moderate, moderately severe, or severe based on the score (**Appendix I**, http://links.lww.com/CCX/B177). COWS and the DSM-V opioid withdrawal criteria have overlap in their assessment of many symptoms; however, there are some key differences: COWS assesses pulse, restlessness, and tremor whereas DSM-V assesses insomnia and fever. Although the critically ill pediatric population has a well described prevalence of IWS (45–68% after 3–5 d of scheduled opioids) and validated tools (e.g., the Withdrawal Assessment Tool 1 and the Sophia Observation Scale), there are no scoring tools validated to identify IWS in critically ill adult patients (12).

With the lack of validated assessment tools, IWS is likely underdiagnosed in critically ill adult patients. To date, the few studies that have been published evaluating the prevalence and risk factors of IWS were mostly conducted in critically ill adult trauma patients with an IWS prevalence of 16.7–44% (9, 13). A recent study evaluated the prevalence of IWS in a mixed ICU patient

population that included 65% medical ICU patients and found a similar prevalence of IWS of 23.6% (14).

There are many unanswered questions regarding IWS in critically ill adult patients, specifically the medically critically ill. The main purpose of this study was to identify the prevalence of IWS in critically ill medical patients who receive continuous opioid infusions for greater than or equal to 24 hours. Additionally, we aimed to identify risk factors associated with IWS. We hypothesized that an increase in cumulative opioid doses, longer durations of therapy, and use of other sedatives would increase the prevalence of IWS.

MATERIALS AND METHODS

This was a prospective, observational study conducted at a large, tertiary teaching hospital assessing IWS based on COWS. The protocol was approved by the institutional review board of Orlando Health Orlando Regional Medical Center in October 2019 (1502772-4; 19.254.09). A waiver of informed consent was granted by the review board as patients were treated per usual care and deemed to be at minimal risk via the study. The study was conducted in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975. The primary objective of the study was to identify the prevalence and risk factors for IWS in patients who were admitted to the critical care medicine (CCM) services from October 2019 to November 2020.

All patients on opioid infusions on the CCM service were identified through the electronic medical record. Patients were eligible for enrollment if they were greater than or equal to 18 years old, admitted to the CCM service, and had received greater than or equal to 24 consecutive hours of continuous opioid infusion. Patients were excluded if they were admitted for any type of drug overdose, had concomitant intracranial pathology, had active COVID-19 at time of assessment, transitioned to withdrawal of life support or hospice, remained Glasgow Coma Scale less than or equal to 8 and/or Richmond Agitation-Sedation Scale (RASS) less than −2 for at least 2 of the 5 assessment days, prisoners, pregnant patients, or if the investigators failed to collect data on greater than or equal to 2 assessment days. Patients were assessed at bedside by an investigator within the next calendar day from opioid infusion cessation and followed once daily for a maximum of 5 days, or until the patient developed severe IWS, expired, or was discharged, whichever occurred first.

The primary outcome was the prevalence of IWS of moderate severity or greater based on COWS. We used this conservative definition to avoid overestimating the prevalence of IWS since the symptoms can be nonspecific and have a large differential diagnosis, especially in critically ill patients. Secondary outcomes included the prevalence of IWS diagnosis of any severity based on COWS, the prevalence of IWS diagnosis based on a positive DSM-V score, and the identification of potential risk factors for developing IWS of any severity. Concomitant drugs given during the opioid infusion that may contribute to withdrawal symptoms, such as sedatives, benzodiazepines, antipsychotics, baclofen, gabapentinoids, and continuous neuromuscular blocking agents (NMBAs) were also examined.

Other datapoints included mean daily dose and cumulative dose of opioids (in fentanyl equivalents), duration of opioid infusion, highest infusion rate at any given time, highest infusion rate within 24 hours before cessation, and time from the highest infusion rate to cessation during the final 24 hours on the opioid infusion. Creatinine clearance less than 30 mL/min at any point during the opioid infusion was also recorded. Baseline characteristics for data collection included principal diagnosis for ICU admission, psychiatric history (bipolar disorder, schizophrenia, depression, and/or anxiety), age, gender, smoking history, positive urine drug screen on admission, prior alcohol or substance abuse history, and prior chronic opioid use.

Sedation practices at our institution follow the analgesia first sedation strategy as recommended by clinical practice guidelines (1). Continuous infusion of opioids were administered first to relieve pain and maintain sedation according to RASS. Pain was assessed using the Critical Care Pain Observation Tool. If additional sedation was needed after adequate pain control, then propofol, dexmedetomidine, or benzodiazepines could be used concomitantly. Choice of additional sedation agent was chosen by the provider based on patient specific factors and disease state optimization. When sedative agents were used in combination with an opioid infusion, sedative agents were weaned off before opioids.

For statistical analysis, the primary outcome was defined as the proportion of patients with an IWS score of moderate or greater. The secondary outcomes, comparing all IWS-positive patients versus IWS-negative

patients, were analyzed using Student *t* test or Mann-Whitney *U* test for normally distributed continuous data. The chi-square or Fisher exact test were used for categorical data. A post hoc analysis comparing IWS-positive patients who received only opioid infusions was also performed to determine if adjunctive medications contributed to IWS. A logistic regression was performed to assess the relationship between the development of IWS and predictor variables. A *p* value of less than 0.05 was considered statistically significant. Final statistical analysis was performed using IBM SPSS Statistics for Windows, Version 26.0. IBM Corp (Armonk, NT).

RESULTS

Between October 15, 2019, and October 31, 2020, a total of 667 patients admitted to the CCM service required continuous opioid infusions. Of these, 477 patients received greater than or equal to 24 hours of opioid infusion and were eligible for enrollment. A total of 385 patients were not included in this trial, as shown in **Figure 1**. Ninety-two patients were included in the final analysis.

Prevalence of IWS

For the primary outcome, 11 patients (12%) experienced IWS of moderate severity or greater based on COWS. Of these 11 patients, nine patients (82%) were also diagnosed with IWS based on the DSM-V criteria. No patients experienced moderately severe or severe IWS based on COWS. For secondary outcomes, 32 patients (35%) experienced IWS, including all severities, based on COWS and 27 patients (29%) experienced IWS based on a positive DSM-V score.

Risk Factors for IWS

The remainder of the secondary outcomes were compared between those that experienced IWS (including all severities) versus those that were negative for IWS. All baseline characteristics were similar between the two groups (**Table 1**).

The mean daily dose of fentanyl infusion, cumulative fentanyl dose, infusion duration, and highest infusion rate at any given time were all significantly greater in the IWS-positive group compared with the IWS-negative group (**Table 2**). The mean daily dose and cumulative dose remained significantly greater in the IWS-positive group when adjusted for weight. There was no significant difference between the two groups when comparing highest infusion rate during the 24 hours before cessation of the fentanyl infusion or the time from highest infusion rate to cessation within that time period.

There was no difference in the overall use of sedatives while receiving opioid infusions. However, when looking into individual sedatives, dexmedetomidine infusions were used significantly more in patients in the IWS-positive group during and/or after opioid continuous infusions (**Table 3**). There was a significant difference in the overall use of concomitant medications; however, this was largely driven by a significantly higher usage of benzodiazepines in the IWS-positive group compared with the IWS-negative group. No other concomitant medications were found to be significant, including the use
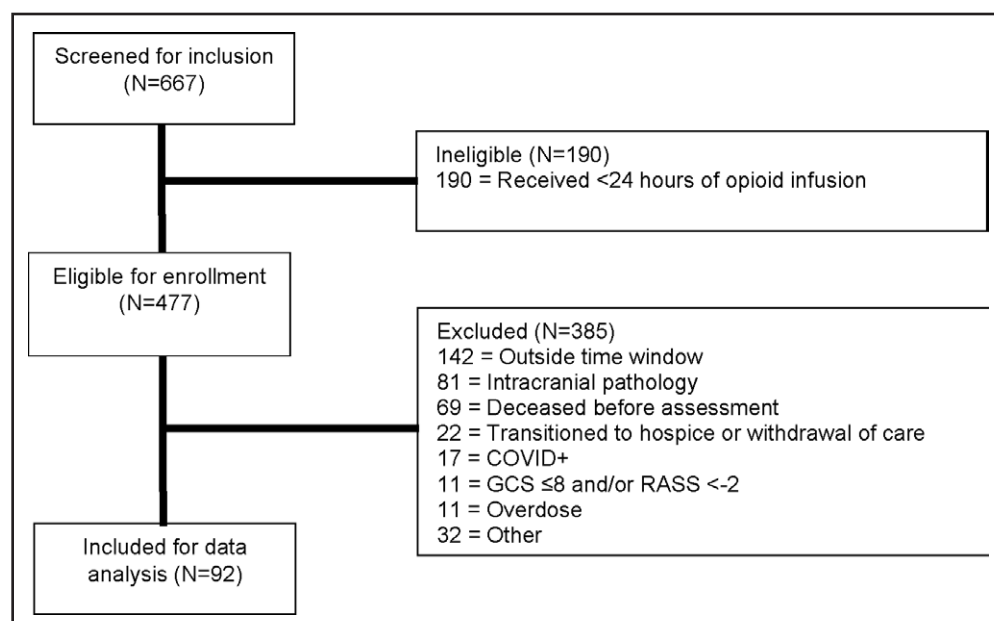

Figure 1. Patient inclusion flowchart.

TABLE 1.
Baseline Characteristics

Characteristics	IWS-Positive (n = 47)	IWS-Negative (n = 45)	p
Median age, yr (IQR)	63 (49–72)	62 (54.5–72)	0.848
Male, n (%)	30 (63.8)	34 (75.6)	0.262
Weight, kg (IQR)	85 (62.3–108)	80.3 (72.4–101)	0.791
Body mass index, kg/m² (IQR)	28.5 (22.8–37.4)	27.3 (23–32.2)	0.687
Medical history, n (%)	13 (27.7)	7 (15.6)	0.159
Anxiety	9 (19.1)	3 (6.7)	0.12
Depression	4 (8.5)	4 (8.9)	1
Bipolar	3 (6.4)	1 (2.2)	0.617
Schizophrenia	3 (6.4)	1 (2.2)	0.617
Principal diagnosis for ICU admission, n (%)			0.139
Cardiac	10 (21.3)	15 (33.3)	
Respiratory	20 (42.6)	17 (37.8)	
Sepsis	10 (21.3)	3 (6.7)	
Other	7 (14.9)	10 (22.2)	
Positive urine drug screen on admission, n (%)	5 (10.6)	3 (6.7)	0.395
Prior alcohol abuse history, n (%)	8 (17)	4 (8.9)	0.355
Prior substance abuse history, n (%)	6 (12.8)	5 (11.1)	1
Prior chronic opioid use, n (%)	5 (10.6)	1 (2.2)	0.204
Smoking history, n (%)	16 (34)	12 (26.7)	0.501
Incidence of ICU delirium, n (%)	21 (44.7)	13 (28.9)	0.117
CrCl < 30 mL/min at any point during opioid infusion, n (%)	22 (46.8)	25 (55.6)	0.414

IQR = interquartile range, IWS = iatrogenic withdrawal syndrome.

of antipsychotics, baclofen, gabapentinoids, or continuous NMBAs.

Because of the differences in concomitant sedative infusions identified, a post hoc analysis was conducted evaluating patients in our cohort who received opioid infusion monotherapy. Twenty-nine patients received opioid monotherapy. Twelve of 29 patients, 41%, experienced IWS according to the COWS assessment. When evaluating opioid characteristics in this cohort, patients in the IWS-positive group had significantly longer opioid infusion durations and a trend toward higher median weight based total daily and cumulative doses (**Table 4**).

Scheduled and as needed (PRN) opioid use up to five days after the cessation of the opioid infusion was also assessed. Only 26% of patients in the IWS-positive group and 13% of patients in the IWS-negative group had scheduled opioids postopioid infusion (**Table 5**). There was a trend toward higher cumulative and total daily doses in the IWS-positive group; however, this was not statistically significant. More patients received PRN opioids in the IWS-positive group compared with the IWS-negative group (57% vs 40%), but no endpoints were statistically significant.

A logistic regression was performed to assess the relationship between the development of IWS and predictor variables, including history of substance use, duration of infusion greater than or equal to 72 hours, and total daily fentanyl dose greater than or equal to 1,200 µg. After controlling for covariates, continuous opioid infusions greater than or equal to 72 hours ($p = 0.043$) and total daily fentanyl dose greater than or equal to 1,200 µg ($p = 0.002$) were found to be independent predictors for the development of IWS.

TABLE 2.
Opioid infusions

Outcome	IWS-Positive (n = 47)	IWS-Negative (n = 45)	p
Median daily dose of opioid infusion, µg	2,050 (1,300–3,437)	650 (388.8–1,708)	< 0.001
Median daily dose of opioid infusion, µg/kg	25 (15–41)	9 (5–21)	< 0.001
Cumulative opioid infusion dose, µg (median)	11,850 (7,020–22,205)	6,000 (2,610–9,102.5)	0.001
Cumulative opioid infusion dose, µg, kg (median)	149 (86–250)	54 (33–117)	< 0.001
Duration of opioid infusion, hr (median)	88 (48–148.2)	45 (33.9–71.5)	< 0.001
Highest infusion rate at any given time, µg/hr (median)	300 (200–400)	200 (150–300)	0.017
Highest infusion rate 24 hr before cessation, µg/hr (median)	150 (100–250)	150 (100–225)	0.442
Time from highest infusion rate within 24 hr to cessation, hr (median)	5 (1–16)	3 (1–12.5)	0.369

IWS = iatrogenic withdrawal syndrome.
All data are reported as mean (SD) or median (interquartile range).
Doses are reported in fentanyl microgram equivalents.

TABLE 3.
Concomitant Medications

Medications, n (%)	IWS-Positive (n = 47)	IWS-Negative (n = 45)	p
Continuous infusion sedative use	35 (74.5)	28 (62.2)	0.263
Dexmedetomidine	18 (38.3)	7 (15.6)	0.014
Propofol	26 (55.3)	20 (44.4)	0.297
Midazolam	16 (34)	14 (31.1)	0.826
Concomitant medications	41 (87.2)	30 (66.7)	0.025
Benzodiazepines	30 (63.8)	17 (37.8)	0.021
Antipsychotics	19 (40.4)	12 (26.7)	0.190
Baclofen	1 (2.1)	2 (4.3)	0.495
Pregabalin	1 (2.1)	0 (0)	1
Gabapentin	6 (12.8)	13 (28.9)	0.073

IWS = iatrogenic withdrawal syndrome.

DISCUSSION

This is the largest study evaluating the prevalence and risk factors for IWS in an exclusive medical critical care patient population. In general, the development of IWS following exposure to continuous opioid infusions during critical illness is an under-appreciated complication. The results of this study suggest that, based on COWS, a significant percentage of patients on continuous opioid infusions for greater than or equal to 24 hours may develop at least mild IWS, and a subset of these patients will develop IWS of moderate severity or greater. Our primary outcome is a conservative depiction of the prevalence of IWS in our patient population as we only included patients with moderate IWS or higher and did not include patients with mild IWS.

Wang et al (13) conducted a prospective, observational, cohort study in trauma ICU patients. They identified an prevalence of IWS of 16.7% using

TABLE 4.
Opioid Infusions in Patients on Monotherapy

Outcome	IWS (*n* = 12)	No IWS (*n* = 17)	*p*
Median daily dose of opioid infusion, µg	1,513.75 (975–2,237.5)	650 (304.75–1,430)	0.232
Median daily dose, weight-based, µg/kg	20.5 (13.25–34)	9 (4–18)	0.06
Cumulative opioid infusion dose, µg (median)	7,350 (3,762.5–13,500)	4,315 (2,676–8,382.5)	0.352
Cumulative dose weight-based, µg/kg	135.6 (48–196.75)	47 (35–90)	0.077
Duration of opioid infusion, hr (median)	71 (33.75–98.5)	45 (37.4–68.3)	0.027
Highest infusion rate at any given time, µg/hr (median)	200 (112.5–237.5)	150 (125–200)	0.586
Highest infusion rate 24 hr before cessation, µg/hr (median)	112.5 (100–200)	100 (100–200)	0.964
Time from highest infusion rate within 24 hr to cessation, hr (median)	2.5 (1–20.25)	10 (1–18.5)	0.607

IWS = iatrogenic withdrawal syndrome.
All data are reported as mean (SD) or median (interquartile range).
Doses are reported in fentanyl microgram equivalents.

TABLE 5.
Maintenance Opioid Dose Postopioid Infusion

Outcome	IWS-Positive (*n* = 47)	IWS-Negative (*n* = 45)	*p*
Scheduled opioids ordered after cessation of opioid infusion, *n* (%)	12 (25.5)	6 (13.3)	0.140
Cumulative scheduled opioid dose, fentanyl equivalence in µg (mean, SD)	800 (345–1,460)	560 (305–747.5)	0.281
Daily mean scheduled opioid dose, fentanyl equivalence in µg (mean, SD)	231 (83.4–333)	112 (61–149.5)	0.174
PRN opioid ordered after cessation of opioid infusion, *n* (%)	27 (57.4)	18 (40)	0.094
Cumulative PRN dose, fentanyl equivalence in µg (mean, SD)	160 (60–300)	162.5 (100–427.5)	0.702
Mean daily dose of PRN, fentanyl equivalence in µg (mean, SD)	60 (18–100)	37.5 (20–85.5)	0.487

PRN = as needed.
Doses are reported in fentanyl microgram equivalents.

DSM-V criteria in patients who were mechanically ventilated and receiving opioids for at least 72 consecutive hours. In 2020, Arroyo-Novoa et al (9) published a prospective, exploratory, observational study conducted in a trauma ICU. The study identified the prevalence of probable opioid and benzodiazepine withdrawal (within 72 hr of medication weaning) as 44% in patients who were expected to receive opioids and/or benzodiazepines for at least 5 days. The large difference in results of these two studies could be beacuse of the prolonged exposure of opioids and/or benzodiazepines in the study by Arroyo-Novoa et al (9) (minimum of 5 d required for inclusion). Our study in medical ICU patients, with an prevalence of IWS of 29% based on DSM-V criteria, was higher than that reported by Wang et al (13) in trauma patients. Most trauma patients in both previously mentioned trials were admitted to the ICU for external causes of morbidity, likely requiring and receiving opioids for pain management after the cessation of continuous opioid infusions. However, most medical patients in our study were admitted to

the ICU for respiratory failure, and the majority of patients did not receive scheduled opioids following the cessation of the continuous opioid infusions postextubation. Thus, we hypothesized that medical ICU patients on continuous infusion opioids could be at an increased risk for IWS compared with surgical ICU patients. The most recent study by Taesotikul et al (14) significantly contributed to the literature by evaluating a mixed ICU patient population which included 36 medical ICU patients and found an prevalence of IWS of 23.5%. The prevalence of IWS in that study is similar to the prevalence of IWS identified in our study when using DSM-V criteria (29%) despite a significantly lower median rate of opioid infusion and slower weaning process with a once daily weaning strategy. Based on studies currently available and the reported prevalence of IWS ranging from 16% to 44%, the need for IWS monitoring postopioid infusion is apparent.

Few trials have identified risk factors for the development of IWS. Wang et al (13) found the cumulative opioid dose and duration of continuous opioid infusions before weaning as potential risk factors for IWS. Additionally, Cammarano et al (15) identified higher rates of withdrawal in patients who received higher daily and peak fentanyl equivalent doses in the trauma ICU. Studies in the PICU population reported similar probable risk factors for IWS (12). Our study was consistent with these results as we found that patients with IWS received greater mean daily doses, cumulative doses, and duration of opioid infusions than those that did not experience IWS. The logistic regression analysis also identified continuous opioid infusions for a duration greater than or equal to 72 hours and total daily fentanyl dose greater than or equal to 1,200 µg as significant risk factors for the development of IWS Additionally, Taesotikul et al (14) identified once daily weaning rate greater than 50 µg fentanyl per hour had nine-fold higher rate of IWS compared with a lower weaning rate. Although we did not directly compare weaning rates in our study, the majority of fentanyl infusions in our study were weaned by greater than 50 µg/hr/d (Table 2).

Currently, there are no validated tools in the adult ICU population for the diagnosis of IWS. Previous studies identifying IWS in adult ICU patients have largely used DSM-V as the assessment tool (9, 13). Although COWS has not been previously studied in critically ill adult patients, it is widely used in the outpatient setting because of its reliability and ease of use (11). COWS may be more objective as it allows the assessor to determine the severity within each category and provides a range of overall scores allowing the diagnoses to be classified from mild to severe. COWS may also have an advantage over DSM-V scale as it incorporates hemodynamic parameters such as resting pulse rate as well as classifying all gastrointestinal distress (nausea, vomiting, and diarrhea) in one category, versus the DSM-V scale scoring each individual component which may overestimate the presence of IWS. The DSM-V scale, on the other hand, may be easier to use as each category is dichotomously scored. Both scales do require some patient participation, which can be difficult in patients in the ICU.

This study has several strengths. It is the largest study evaluating the prevalence and risk factors for IWS in exclusively medical critical care patients. Additional strengths include the prospective design and a conservative primary outcome of IWS of moderate severity or greater. Since there is no validated tool to assess IWS in adult critical care patients, the study used two assessment tools, DSM-V and COWS, to try to accurately describe the prevalence of IWS and potentially introduce another scoring tool that may be useful in clinical practice.

The study also has several limitations, the first being its small sample size. Also, due to operational challenges, there were instances in which some patients did not have daily assessments completed, as well as the fact that patients were only screened for inclusion from Monday to Friday. Assessor bias may have also influenced the results as each patient was only assessed by one clinician. Lastly, a higher percentage of the IWS-positive group required additional sedatives during or after continuous opioid infusion, particularly dexmedetomidine and benzodiazepines. When evaluating patients on opioid monotherapy, there was a higher prevalence of iatrogenic opioid withdrawal, and opioid dosing and duration remained similar to our total population which illustrates that our results are likely related to opioid withdrawal instead of dexmedetomidine or benzodiazepine withdrawal. However, it is possible that these concomitant medications may have masked the signs and symptoms of IWS if administered at the time of assessment. Further investigation

is needed to evaluate the correlation and effect of sedatives and benzodiazepines on IWS.

As our findings reveal, prolonged duration of opioid infusions (≥ 72 hr) and total daily fentanyl dose greater than or equal to 1,200 µg are risk factors for the development of IWS. Additionally, overall exposure to opioid infusions, specifically high cumulative doses, may be risk factors for the development of IWS. The clinical impact on long-term outcomes such as ICU or hospital length of stay and long-term opioid dependence need to be further investigated. This study draws attention to the issue, but further studies with larger sample sizes are required to fully elucidate the consequences of IWS in medical critical care patients and its recommended treatment strategies.

CONCLUSIONS

Approximately one in every eight patients receiving continuous infusion opioids for greater than 24 hours while mechanically ventilated in the medical ICU will develop IWS of moderate severity or greater. When using DSM-V or any severity of IWS on COWS this increases to 1 in every 3 patients, illustrating that IWS is a significant concern in medical ICU patients when continuous infusion opioids are discontinued. Consistent with prior studies, IWS-positive patients received higher daily and cumulative doses of opioids, longer durations of opioid infusion, and higher continuous infusion rates. Patients receiving opioid infusions greater than or equal to 72 hours, or a total daily fentanyl dose of greater than or equal to 1,200 µg (~ 50 µg/hr) are at a higher risk for developing IWS, and therefore, clinicians should routinely assess for its occurrence upon opioid infusion discontinuation in patients meeting these parameters.

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