Opioid, sedative, pre-admission medication and iatrogenic withdrawal risk in UK adult critically ill patients: a point prevalence study

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Abstract

Background: Iatrogenic withdrawal syndrome, after exposure medication known to cause withdrawal is recognised, yet under described in adult intensive care.

Aim: Investigate, opioid, sedation and preadmission medication practice in critically ill adults with focus on aspects associated with iatrogenic withdrawal syndrome

Methods: One-day point prevalence study in UK ICUs. We collected ICU admission medication and/or substances with withdrawal potential, sedation policy, opioid and sedative use, dose, and duration.

Results: 37 from 39 participating ICUs contributed data from 386 patients. The prevalence rate for parenteral opioid and sedative medication was 56.1%, (212 patients). 23 ICUs (59%) had no sedation/analgesia policy, and no ICUs screened for iatrogenic withdrawal. Patient admission medications with withdrawal-potential included antidepressants or antipsychotics (43, 20.3%) and nicotine (41, 19.3%). Of 212 patients, 202 (95.3%) received opioids, 163 (76.9%) sedatives and 153 (72.2%) both. 202 (95.3%) patients received opioids: 167 (82.7%) by continuous infusions and 90 (44.6%) patients for longer than 96-hours. 163 (76.9%) patients received sedatives: 157 (77.7%) by continuous infusions and 74 (45.4%) patients for longer than 96-hours.

Conclusion: Opioid and sedative prevalence rates were high, and a high proportion of ICUs had no sedative/analgesic policies. Nearly half of patients received continuous opioids and sedatives for longer than 96-hours placing them at high risk of iatrogenic withdrawal. No participating unit reported using a validated tool for iatrogenic withdrawal assessment.

Impact Statements

Opioid and sedative prescribing prevalence was high; and approximately 50% of patients prescribed opioid and/or sedative continuous infusion for greater than 96 hours.

Patients were at high risk of iatrogenic withdrawal.

There were no validated tools for iatrogenic withdrawal assessment.

A high proportion of participating ICUs did not have a sedation and analgesia policy.

Healthcare professionals should be aware of potential for iatrogenic withdrawal in patient assessment.

Introduction

Patients admitted to the intensive care unit (ICU) frequently receive opioids and sedatives for treating pain and anxiety and to facilitate effective mechanical ventilation[1]. The longer that patients receive mechanical ventilation with opioids and sedatives, the higher the risk of delirium some of which may

represent iatrogenic withdrawal syndrome (IWS) [2]. IWS manifests with a combination of signs and symptoms due to dysregulation of the autonomic nervous system. These symptoms occur upon abrupt discontinuation or rapid tapering of drugs known to produce physiological dependence and the syndrome shares features of both sedative-hypnotic and opioid withdrawal [3].Signs of IWS overlap with delirium secondary to critical illness; and it is therefore challenging to diagnose IWS in critical illness without a validated assessment tool [4, 5].

In children, IWS is well described and associated with untoward outcomes such as an increased duration of mechanical ventilation, ICU, and hospital length of stay [5, 6] . IWS is largely unrecognised in adult intensive care and this under-recognition in adults may be due to challenges understanding the problem, its overlap with other conditions, lack of screening tools and management strategies, and it's unclear impact on clinical outcome [1]. Risk factors could include prolonged and cumulative doses of opioids and benzodiazepines, prolonged duration of sedative use, high body mass index, young age, and a history of drug or alcohol dependence [2, 7].

International guidelines recommend assessment-driven, protocol-based strategies to manage pain and sedation and prevent complications, including IWS (conditional recommendation, moderate quality evidence[1] . Within the UK, two previous sedation surveys of 214 and 157 adult ICUs respectively reported that 57 and 59% had a written sedation protocol; 94% and 78% had sedation hold policies [8, 9]. The use of IWS protocols were not reported. Furthermore, the publication of the 2018 Society of Critical Care Medicine guidelines for pain, agitation/sedation, delirium, immobility, and sleep disruption (PADIS) in adult patients in the ICU do not address IWS [1]. Clearly there are gaps in understanding of assessment, prevention, and treatment of IWS.

The aim of this study was to investigate current opioid, sedation and preadmission medication practice in critically ill adults with a focus on aspects that could relate to IWS. The study objectives were to describe how adult ICU patients were weaned from continuously administered opioids and sedatives; compare those ICUs with and without a sedation policy; compare equivalence in patient opioid burden, and describe opioids and sedatives used in participating ICUs. Furthermore, we hoped to identify if assessments were conducted to identify IWS and whether validated tools were used.

Ethical considerations

The ALERT-ICU protocol was reviewed by the Wilkes University Institutional Review Board (IRB) [Ref: #116] and was provided an ethical exempt determination notification. In the UK, the study was classified as a service evaluation, reviewed by local Research and Development Offices in participating hospitals and Data Use Agreement and Institutional Authorisation Agreements were approved.

Methods

This UK study was part of an international point prevalence study. The study was registered on ClinicalTrials.gov (AduLt iatrogEnic withdRawal sTudy in the ICU [ALERT-ICU], Bolesta 2021, NCT04422808). The study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.

Study design and participants

A prospective, observational, one-day point prevalence study of opioid, sedation, and drug withdrawal practices in National Health Service, NHS UK ICUs. ICUs selected a one-day study period between June 1st and September 30th, 2021. Patients aged 18-years and older admitted to adult ICUs were eligible for inclusion. Patients were included if they received either parenteral opioids and/or sedatives in the 24-hours prior to the data collection day.

All electronic study data were kept in password-protected computer files. Data were coded by assigning a unique identification number to participating institutions and individual ICUs. and patients were assigned a unique study identification number. Analysis was performed using the coded data. Only aggregate data without personal identifiers have been included in results.

Data collection

We engaged with national representatives from professional networks including the UK Clinical Pharmacy Association (UKCPA), the Intensive Care Society (ICS), and the UK Critical Care Research Group (UKCCRG). Networks advertised the study on a national level and recruited members as investigators. The local investigators liaised with their Research and Development Offices to secure approval, collected data and acted as guarantor for the integrity and quality of data. To maximise consistency in reporting, registered local investigators received training on data collection through virtual meetings (led in UK by RE), and online tutorials, recorded training sessions and the Operations Manual available on the ALERT-ICU website (https://www.iatrogenicwithdrawalstudy.com/).

Anonymous patient data were collected using the Research Electronic Data Capture (Redcap) secure web-based data collection tool. The system allowed real-time input of data by local investigators.

Data were collected pertaining to ICU type, its daily multidisciplinary ward rounds, use of opioids, sedation, admission drugs with withdrawal potential and withdrawal assessment tools and protocols. Patient characteristics and clinical data were obtained from the patient's clinical record. Daily and cumulative amounts of opioids and sedatives were recorded along with durations of therapy and medication weaning. Patient hours on mechanical ventilation and length of ICU stay were also documented up to point of data collection.

Medicines reconciliation data

History of recreational substance use and long-term medication with a documented predisposal to withdrawal syndrome were also collected [10]. This included information about prescription of gabapentinoids, antidepressants, opioids, and history of nicotine (including tobacco), alcohol and other drug use.

Data analysis

Data were analysed by RE, DH and BB using appropriate descriptive statistics (number, proportion; mean, standard deviation; or median, interquartile range) and are presented in tabular format. Opioid and sedative doses were expressed as total in milligrams on day of data collection. We explored relationships between units that did/did not have sedative and opioid analgesia policies in types of analgesia and sedatives used, dosages, and reduction in dosage percentages using Chi square and Mann-Whitney U using Social Science Statistics. (https://www.socscistatistics.com/tests/chisquare2/default2.aspx).

For comparison purposes, we expressed opioid doses in terms of fentanyl equivalence [11]. For sedation therapy, we were unable to calculate equivalent dosing because the selected sedatives had different pharmacological properties e.g., benzodiazepines and alpha-2-agonists; therefore, we used sedative duration to compare sedatives.

Results

ICU and patient characteristics

39 ICUs from 17 UK NHS Trusts participated, and 212 of 378 screened patients (56.1%) from 37 ICUs met inclusion criteria and were included in the study (Table 1). The major ICU type was mixed medical/surgical (59%). Multidisciplinary bedside rounds were conducted in most (33, 84.6%), and were conducted a minimum of four times per week in 17 ICUs (43.6 %). A minority of ICUs reported policies that addressed daily sedation interruption (17 ICUs, 43.6%), general sedation/analgesia (14 ICUs, 36%), sedation/analgesia weaning (8, 20.5%), and IWS 4 (10.3%). All ICUs reported having tools to assess the level of sedation only three units did not use a pain assessment tool. None of the 39 ICUs reported a validated tool to assess for IWS.

A greater proportion of patients were admitted with respiratory system disease (79, 37.3%) and were white (162, 76.4%) (Table 2). At the point of recruitment, patients had been in the ICU for a median of 6 (IQR 2 to 14) days; 165 (78.3%) were receiving invasive mechanical ventilation; and 54 (25.5%) were COVID-19 positive.

The main medications with iatrogenic withdrawal potential taken by patients prior to admission were antidepressants or antipsychotics (20.3%) and opioids (14.2%), with 41 (19.3%) taking nicotine and 12 (5.7%) with a history of taking recreational drugs (Table 2). Alcohol dependence was noted in 25 (11.8%) patients.

In the 24-hours prior to data collection, 202 patients (95.3%) received parenteral opioids; 163 (76.9%) received parenteral sedatives; and 153 (72.2%) received both.

Opioids

Of 202 patients who received parenteral opioids the most used were fentanyl (35.1%) and alfentanil (33.2%) (**Table 3**). There were 167 (83%) patients who received opioids by continuous infusion and 44.6% received opioids for more than 96 hours. Of 150 patients who received opioids for 24 hours or more, 36.3% had the dose reduced within the previous 24 hours. Most of these, (16 patients, 29.6%) had their dose reduced by more than 50%. 171 (84%) patients were receiving the shorter acting opioids, remifentanil, alfentanil and fentanyl.

Within the 14 ICUs that had a sedation/analgesia policy in place there were more patients on fentanyl and less patients on alfentanil and morphine (X^2 36.87 [df 3], N = 186, p = <.001). No patients in ICUs with a policy received oxycodone in comparison to 20 patients in non-policy ICUs. In patients with opioid duration of 24 hours or more; there was no relationship between policy/no policy ICUs and opioid duration (X^2 1.99 [df 3], N = 202, p =.57) or the proportionate reduction in opioids over the previous 24-hours (X^2 4.37 [df 3], N = 54, p =.36).

Higher doses of fentanyl as continuous infusion were administered to patients in ICUs with no sedation/analgesia policy in comparison to those with a policy (Mann-Whitney test (two-tailed) N=71, p=0.047. In contrast, doses of alfentanil doses were higher in ICUs with a sedation/analgesia policy and these ICUs recorded higher total overall opioid exposure (Mann-Whitney test (two-tailed) alfentanil, N=67 p=0.0029. All opioids were converted into an equivalent dose of fentanyl. Median alfentanil doses were approximately 3.3 times higher, and remifentanil doses 7 times higher, than fentanyl, morphine was equivalent, and oxycodone was 0.5 less [11].

Sedatives

Of 163 patients who received sedatives, the most common was propofol (83.4%), then midazolam (20.2%) (**Table 4**). The main method of administration was continuous infusion, and 45.4% of patients received sedatives for more than 96 hours. Of 120 patients receiving sedatives for 24 hours or more, 36.7% patients had a reduction in dosage and 14 (31.8%) had their dose reduced by more than 50%.

There was no significant relationship between policy/no policy ICUs and types of sedative used(X^2 1.42 [df 4], N = 197, p = .84), duration of sedative use (X^2 1.3 [df 3], N = 163, p =.73), or the proportionate reduction over the previous 24-hour period (X^2 1.7 [df 3], N = 41, p =.62). In patients receiving sedatives for greater than 72 hours, there was a later increase in alpha-2-agonists and midazolam use. (Table 5, Supplementary File 2).

Medicines reconciliation data

Of the 212 patients, there were 178 pre-ICU admission historical prescriptions for medications associated with a withdrawal syndrome, or a medical history of alcohol , nicotine, or substance dependence [10].The overall prescription rate was 0.47 per included patient. The highest rate was for antidepressants/antipsychotics at 20.3%, followed by nicotine dependence (including tobacco) in 19.3% of patients, followed by long term opioids (14.2%), and 11.8% had a report of alcohol dependence.

Discussion

This prospective, observational, one-day point prevalence study reported: (1) high exposure of ICU patients to continuous infusions of opioids and sedatives, with over 50% of participants receiving continuous sedation or opioids for more than 72 hours; (2) a higher incidence of opioid than sedative administration; (3) heterogenous practice relating to sedation and opioid use, including medication choice and weaning strategies; (4) an absence of validated tools to allow identification and treatment of IWS; (5) limited use of policies or protocols to guide sedation and opioid practice; and (6) high prevalence of preadmission substances and medication known to cause a withdrawal syndrome.

This study gives contextual information for IWS in the adult ICU population; and gives evidence for IWS risk in adults. The majority of IWS research literature has been derived work conducted in the paediatric critical care population, where IWS is recognised, assessed with validated tools;

(benzodiazepine and opioid withdrawal scale (SOPHIA) clinical opioid withdrawal scale (COWS), and managed with longer acting opioid agents including methadone [6, 7]. In the paediatric critical care literature, children exposed to opioids or sedatives for greater than 72 hours are deemed at IWS risk [3]. In the context of this point prevalence, almost half of included patients could be at risk of developing IWS[3]. Finally, the study was conducted in 39 UK ICUs and therefore gives a broad perspective of IWS risk and include preadmission medication, and prevalence of opioid and sedative exposure.

There were limitations to the point prevalence data; 78 (ICUs originally offered to participate with only 39 (50%) ICUs finally contributing their data. One in four of ICU admissions were admitted with Covid-19 related pathophysiology and could make our data less representative of ICU admissions during a non-pandemic time. We did not collect relevant clinical outcome data after the day of point prevalence including duration of mechanical ventilation of ICU length of stay. Alcohol and nicotine dependence is widely acknowledged to be underreported [12]. Finally, our data was derived using observational point prevalence methodology and dependent on patient demographic and opioid/sedation data on the day of data collections and had a high risk of selection bias.

The proportion of opioid administration was high in patients in comparison to sedatives. Whether or not this is a consequence of recent guidelines [SCCM 2018] that recommend that pain is treated before considering sedation is difficult to establish [1]. An assessment driven, protocol-based approach to pain and sedation management is recommended in PADIS [1]. Such an approach was not evident in our

findings that reported less than half of ICUs had interprofessional rounds, just over a third had general policies for sedation and analgesia, and very few ICUs with guidelines for weaning medications, and monitoring for signs of IWS. The lack of monitoring is contrary to the general view that during the reduction of sedative-analgesic medications, patients should be closely monitored for acute withdrawal phenomenon [13]. Indeed, no ICUs use a validated IWS screening tool.

In this dataset, five different opioids were administered mainly by continuous infusion (alfentanil, fentanyl, morphine, remifentanil, and oxycodone). For ease of comparison, all were converted into fentanyl equivalence [11]. Our findings suggest that the shorter acting the opioid is, the greater the fentanyl equivalence. Remifentanil's median fentanyl equivalent was seven times greater, alfentanil 3.3 times more than fentanyl, morphine approximately equivalent and oxycodone appearing to be about half [14] .These findings align with opioid potency and μ receptor affinity where the higher the affinity, the greater the dose, the higher overall opioid exposure to patient and potential higher risk of IWS [15, 16].

Accepting the bias of observation data collected using single day point prevalence methodology; we purport these findings give evidence of high risk of IWS in adult ICU patients, and this risk could be higher in patients exposed to -short acting opioids with greater affinity for the μ receptor [14, 16]. This concurs with a retrospective cohort study of 126 patients treated with remifentanil (n = 58), fentanyl (n = 47), or morphine (n = 21), where IWS was seen in 31.0%, 36.2%, and 9.5% of patients, respectively (P = 0.078) [17].

Close to half (44.6%) of patients receiving opioids had a continuous infusion for 96 hours or more. With a dose reduction in the previous 24 hours in only 3 (5.6% patients). Thus, if most patients were on short acting agents (n = 171 (84%) for 96 hours or greater; what could this mean for IWS risk? In 2021, Maffei et al assessed risk factors for IWS in an adult Covid19 ICU population; the multivariable model showed each additional day of IV opioid therapy was associated with an 8% increase in odds of IWS (95% CI, 1.02–1.14)[5]. They concluded prolonged and high dose exposures to IV opioids and benzodiazepines should be limited when feasible [5]. Further, Arroyo et al reported that in 50 ICU patients receiving benzodiazepines and/or opioids, of which 84% of patients were taking a mixture of midazolam (84%) and lorazepam (70%), probable withdrawal syndrome occurred in 55% of patients [2]

With respect to sedatives, propofol was the most used agent in (n = 136 (85%) of patients. This concurs with international sedative guidance (e.g., PADIS 2018) [1]. What was perhaps surprising was one in five patients were receiving midazolam given that international guidelines advise benzodiazepines, especially midazolam and lorazepam, be avoided whenever feasible because of risk of delirium and oversedation [18, 19]. Our findings could have been impacted by the high prevalence (25.2%) of ICU Covid-19 admissions during data collection. Greater amounts of benzodiazepines and more challenging sedation are reported in Covid19 ICU admissions by Pun et al in 2020 and Hanks et al in 2022 [20, 21]. IWS was reported after benzodiazepines by Maffei et al, the risk being 3 times higher after receiving lorazepam (95% CI 1.12 to 8.15 [5].

As for pre-ICU admission IWS risk factors were present in almost 50% of patients (47%), these were alcohol or nicotine dependence or presence of chronic medication that have withdrawal symptoms on cessation including gabapentinoids and antidepressants [5]. We speculate that most patients would have had these medications withheld on ICU admission (especially if the oral or enteral route is not available) and this could contribute to IWS [22].

Future research should include: (1)Development and validation of tools for WS detection in adult ICU patients (2) Establish whether use of short acting opioids including remifentanil and alfentantil increases likelihood of IWS and (3) Ascertain if greater use of alpha-2-agonists over propofol and benzodiazepines, known to manage opioid, alcohol and nicotine, reduce likelihood IWS [23, 24].

Conclusion

In this prospective, observational, one-day point prevalence study conducted in 39 National Health Service UK ICUs' we report a high incidence of opioid and sedation prescribing, with almost half of ICU admissions receiving opioids for over 96 hours; and high prevalence of preadmission medication and substances with withdrawal potential. Thereby increasing the risk of IWS in adult ICU.

Declarations

Acknowledgments

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Competing Interests

Dr McKenzie reports an honorarium for her work as editor in chief for Critical Illness (www.medicinescomplete.com) published by the Pharmaceutical Press. The authors report no additional competing interests.

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necessarily those of the National Institute for Health and Care Research or the Department of Health and Social Care.

Author Contributions

Scott Bolesta devised, conceived, and led the international study AduLt iatrogEnic withdRawal in The Intensive Care Unit (ALERT-ICU) (https://www.iatrogenicwithdrawalstudy.com/). Rebekah Eadie led the investigators UK arm of ALERT-ICU . Rebekah Eadie Daniel Hadfield, Bronagh Blackwood, Cathrine McKenzie and Nicola Kalk designed the methodology and conducted the analyses. The first draft of the manuscript was written by Cathrine McKenzie, all authors commented and revised previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The datasets generated during and/or analysed during the current study are available from authors Rebekah Eadie and Scott Bolesta on reasonable request.

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Tables

Table 1. ICU speciality, interprofessional ward rounds, policy and assessment tools

	No (%)
ICUs	39
ICU patient type	
Mixed medical/surgical	23 (59.0)
Neurological	5 (12.8)
Cardiothoracic surgery	5 (12.8)
Medical	3 (7.7)
General surgical	1 (2.6)
Other	2 (5.1)
Interprofessional bedside rounds	
>/= 4 days/week	17 (43.6)
Daily	14 (36.9)
<4 days/week	1 (2.6)
None	6 (15.4)
Sedation and analgesia policies/protocols	
Daily sedation interruption	17 (43.6)
General sedation/analgesia policy, with/without daily interruption	14 (35.9)
Sedation/analgesia weaning	8 (20.5)
IWS policy to monitor signs/symptoms	4 (10.3)
Assessment tools	
Sedation	39 (100)
Pain	36 (92.3)
Withdrawal	0

Table 2. Patient characteristics

Patients (from 37 ICUs)	212
Female	79 (37.7)
Age, median (IQR) [a]	58.0 (44.0 – 68.0)
BMI, kg/m^2, median (IQR) [b]	27.3 (23.5 – 31.9)
Days in ICU prior to data collection, median (IQR)	6.0 (2.0 – 14.0)
Ethnicity	
Caucasian	162 (76.4)
Asian	14 (6.6)
Black/African	13 (6.1)
Other	3 (1.4)
Unknown	20 (9.4)
COVID-19 status	
PCR positive	54 (25.5)
Reason for ICU admission	
Respiratory system disease	79 (37.3)
Circulatory system disease	37 (17.5)
Nervous system disease	28 (13.2)
Digestive system disease	27 (12.7)
Other	27 (12.7)
Preadmission medications	
Antidepressants/antipsychotics	43 (20.3)
Opioids	30 (14.2)
Paracetamol	22 (10.4)
Gabapentin or Pregabalin	18 (8.5)
Non/benzodiazepine sleeping medication	10 (4.7)
NSAIDs	7 (3.3)
Preadmission nicotine, alcohol and recreational drug use	
Nicotine	41 (19.3)
Alcohol misuse	25 (11.8)

Recreational/illicit drugs	12 (5.7)
Mechanical ventilation treatment in the ICU	
Invasive mechanical ventilation	165 (77.8)
Non-invasive ventilation	8 (3.8)
Parenteral opioid and sedative use over previous 24 hours (inclusion criteria)	
Opioid	202 (95.3)
Sedative	163 (76.9)
Received BOTH opioid and sedative	153 (72.2)
Received ONLY opioid	49 (23.1)
Received ONLY sedative	10 (4.7)

Patients were recruited from 37 out of the 39 ICUs

Data are number (%) of patients unless otherwise stated.

IWS = Iatrogenic Withdrawal Syndrome; IQR = Interquartile Range; BMI = Body Mass Index; PCR = Polymerase Chain Reaction

[a] n = 191; missing data for 21 patients

[b] n = 178; missing/unknown = 34

Table 3. Opioid use over 24 hours

	All	ICU with sedation policy	ICU without sedation policy
Patients receiving opioids, N (%) [a]	*202*	*78*	*124*
Fentanyl	71 (35.2)	49 (62.8)	22 (17.7)
Alfentanil	67 (33.2)	15 (19.2)	52 (41.9)
Remifentanil	33 (16.3)	13 (16.7)	20 (16.1)
Oxycodone	20 (9.9)	0	20 (16.1)
Morphine	15 (7.4)	2 (2.6)	13 (10.5)
Tramadol	2 (1.0)	0	2 (1.6)
Methadone	1 (0.5)	0	1 (0.8)
Methods of administration, N (%) of patients receiving opioids via each route [a, b]			
Continuous IV infusions	167 (82.7)	68 (87.2)	99 (79.8)
PCA	21 (10.4)	8 (10.3)	13 (10.5)
Non-scheduled intermittent	11 (5.4)	0 (0)	11 (8.9)
Scheduled intermittent	7 (3.5)	1 (1.3)	6 (4.8)
Regional anaesthesia	2 (1.0)	1 (1.3)	1 (0.8)
24-hour dose via continuous IV infusion, mg, Median (IQR)			
Fentanyl	2.9 (1.4 – 4.8)	3.5 (1.7 – 5.5))	1.9 (0.8 – 3.9)
Alfentanil	48.0 (32.5 – 92.0)	96.0 (38 – 120)	43.0 (25.3 – 65.9)
Remifentanil	16.1 (4.8 – 21.7)	14.6 (5.3 – 24.8)	16.1 (4.4 – 18.5)
Oxycodone	50.5 (40.0 – 61.0)	0 (0)	50.5 (40.0 – 61.0)
Morphine	208.0 (66.0 – 240.0)	344.0 (208.0 – 480.0)	144.0 (5.0 – 240.0)
Fentanyl equivalent 24-hour dose via continuous IV infusion, Median (IQR) [c]			
Fentanyl	2.9 (1.4 – 4.8)	3.5 (1.7 – 5.5))	1.9 (0.8 – 3.9)
Alfentanil	9.6 (6.5 -18.4)	19.2 (7.6 -24)	8.6 (5.1-13.2)
Remifentanil	20.3 (10.1-41.6)	24.5 (11.9-38.5)	13.3 (5.6-27.3)
Oxycodone	1.4 (1.1-1.6)	0	1.3 (1.1-1.6)

Morphine	2.8 (0.9-3.2)	4.6 (2.8-6.4)	1.9 (0.1-3.2)
Duration of opioid treatment to the point of data collection			
< 24 hours	52 (25.7)	23 (29.5)	29 (23.4)
24 to 72 hours	47 (23.3)	15 (19.2)	32 (25.8)
72 to 96 hours	13 (6.4)	4 (5.1)	9 (7.3)
>96 hours	90 (44.6)	36 (46.2)	54 (43.5)
Opioid reduction in previous 24 hours [d]			
Yes	54 (36.0)	23 (41.8)	31 (32.6)
Reduction % in previous 24 hours [d]			
< 10%	3 (5.6)	1 (4.3)	2 (6.5)
10-20 %	12 (22.2)	7 (30.4)	5 (16.1)
21-30%	12 (22.2)	5 (21.7)	7 (22.6)
31-50%	11 (20.4)	2 (8.7)	9 (29.0)
> 50%	16 (29.6)	8 (34.8)	8 (25.8)
Enteral opioids started in previous 24 hours [d]			
Yes	11 (5.4)	7 (63.6)	4 (36.4)

Data are number (%) of patients, unless otherwise stated

[a] Numbers different to column total as some patients received more than one type of opioid

[b] PCA = Patient Controlled Analgesia (subcutaneous); Non-scheduled intermittent refers to one-off or as needed intravenous, subcutaneous or intramuscular doses; Scheduled intermittent refers to single, non-continuous intravenous, subcutaneous or intramuscular doses administered according to a schedule.

[c] Fentanyl equivalent conversion:

[d] Only patients receiving opioids for 24 hours or more

Table 4. Sedative use over 24 hours

Variable	All	ICU with sedation policy	ICU without sedation policy
Patients receiving sedatives, N (%) [a]	163	64	99
Propofol	136 (83.4)	57 (89.1)	79 (79.8)
Midazolam	33 (20.2)	12 (18.8)	21 (21.2)
Clonidine	17 (10.4)	5 (7.8)	12 (12.1)
Dexmedetomidine	9 (5.5)	3 (4.7)	6 (6.1)
Ketamine	2 (1.2)	1 (1.6)	1 (1)
Lorazepam	3 (1.8)	0 (0)	3 (3)
Methods of administration, N (%) of patients receiving sedatives via each route [a, b]			
Continuous infusion	157 (77.7)	63 (98.4)	94 (94.9)
Scheduled intermittent	7 (3.5)	2 (3.1)	5 (5.1)
Non-scheduled intermittent	5 (2.5)	1 (1.6)	4 (4.0)
Cumulative 24-hour dose via continuous IV infusion, (mg), median (IQR)			
Propofol	2680.0 (1000.0 – 4520.0)	2840.0 (960.0 – 4697.5)	2600.0 (1050.0 – 4520.0)
Midazolam	158.0 (99.4 – 240.0)	191.5 (95.8 – 240.0)	144.0 (99.4 – 238.0)
Clonidine	1.1 (0.4 – 2.5)	0.4 (0.3 – 2.2)	1.3 (0.9 – 2.9)
Dexmedetomidine	2.0 (0.9 – 2.3)	2.0 (0.7 – 2.4)	1.7 (0.9 – 2.5)
Ketamine	230.0 (230.0 – 230.0)	230.0 (230.0 – 230.0)	–
Duration of sedative treatment to the point of data collection			
< 24 hours	43 (26.4)	16 (25.0)	27 (27.3)
24 to 72 hours	36 (22.1)	12 (18.8)	24 (24.2)
72 to 96 hours	10 (6.1)	5 (7.8)	5 (5.0)
>96 hours	74 (45.4)	31 (48.4)	43 (43.4)
Sedative reduction in previous 24 hours [c]			
Yes	44 (36.7)	19 (29.7)	25 (25.3)
Reduction % in previous 24			

hours [c]			
< 10%	3 (6.8)	0 (0)	3 (12.0)
10-20 %	10 (22.7)	6 (31.6)	4 (16.0)
21-30%	7 (15.9)	2 (10.5)	5 (20.0)
31-50%	10 (22.7)	5 (26.3)	5 (20.0)
> 50%	14 (31.8)	6 (31.6)	8 (32.0)
Enteral sedative started in previous 24 hours [c]			
Yes	11 (9.2))	4 (21.1)	7(28.0)

Data are number (%) of patients, unless otherwise stated

[a] Numbers different to column total as some patients received more than one type of opioid

[b] PCA = Patient Controlled Analgesia (subcutaneous); Non-scheduled intermittent refers to one-off or as needed intravenous, subcutaneous or intramuscular doses; Scheduled intermittent refers to single, non-continuous intravenous, subcutaneous or intramuscular doses administered according to a schedule.

[c] Only patients receiving opioids for 24 hours or more

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryfile1.Table5.docx
- Supplementaryfile2.Listofinvestigators.docx