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Impact of the 2018 Society of Critical Care Medicine Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Guidelines on Nonopioid Analgesic Use and Related Outcomes in Critically Ill Adults After Major Surgery

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ABSTRACT: We compared ICU nonopioid analgesic use, opioid use, and pain before and after Pain, Agitation/Sedation, Delirium, Immobility, and Sleep guideline publication at one academic center among critically ill adults receiving an opioid infusion and greater than or equal to 24 hours of mechanical ventilation after major surgery. The 2017 ($n = 77$) and 2019 ($n = 57$) groups were similar at baseline. The 2019 (vs 2017) patients were more likely to receive scheduled IV/oral acetaminophen (84% vs 69%; $p = 0.05$), less likely to receive a lidocaine patch (33% vs 50%; $p = 0.05$), and just as likely to receive ketamine (4% vs 3%; $p = 1.0$), an nonsteroidal anti-inflammatory drug (7% vs 3%; $p = 0.26$), or gabapentin/pregabalin (16% vs 9%; $p = 0.23$). Daily average opioid exposure (in IV morphine milligram equivalent) was not different (70 [42–99] [2017] vs 78 mg [49–109 mg]; $p = 0.94$). The 2019 (vs 2017) group spent more ICU days with severe pain ($p = 0.04$). At our center, Pain, Agitation/Sedation, Delirium, Immobility, and Sleep guideline publication had little effect on nonopioid analgesic or opioid prescribing practices in critically ill surgical adults.

KEY WORDS: acetaminophen; analgesic; intensive care; opioid; pain; surgical

To the Editor:

Pain is common after major surgery in critically ill adults and has traditionally been managed with opioids despite concerns these agents may hinder liberation from mechanical ventilation and increase constipation, delirium, hyperalgesia, and post-ICU opioid use (1–4). Multimodal analgesia, the protocolized use of nonopioid analgesic (e.g. acetaminophen, ketamine, neuropathic medication, and nerve blocks) agents to improve pain and reduce opioid use are key components of Enhanced Recovery After Surgery (ERAS) protocols (5). While multimodal analgesia use is well established after major surgery, its use remains poorly characterized in postsurgical critically ill adults who require continuous opioid infusions and multiple days of mechanical ventilation (1). The 2018 Society of Critical Care Medicine Pain, Agitation/Sedation, Delirium, Immobility, and Sleep (PADIS) guidelines recommend the use of a multimodal analgesic approach (with acetaminophen, ketamine, and neuropathic agents [e.g., gabapentin or pregabalin]) for post-surgical ICU (SICU) pain control (6).

However, data regarding the impact of PADIS publication on nonopioid analgesic use in critically ill surgical patients has not been published. The evidence supporting PADIS nonopioid analgesic use is based on the evaluation of single nonopioid analgesic agents (vs combined analgesics using a multimodal

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approach) and in postoperative patients, most of who transitioned through the ICU quickly. Little current data exists on multimodal analgesia prescribing practices in postsurgical adults admitted to the ICU with critical illness, whether publication of the 2018 PADIS guidelines has influenced these practices (6), and how multimodal nonopioid analgesia use affects clinical outcomes (1, 6). We compared ICU nonopioid analgesic use (in the context of PADIS recommendations), daily opioid use, daily pain scores, and common clinical sequelae associated with ICU opioid use in critically ill surgical adults before and after publication of the PADIS guidelines.

MATERIALS AND METHODS

This retrospective cohort study, approved by the Mass General Brigham Institutional Review Board (2019P003706), evaluated consecutive adults undergoing major surgery during two different years: 2017 (before-PADIS publication) and 2019 (after-PADIS publication) who required postoperative admission to either the surgical, trauma, or thoracic ICU at Brigham and Women's Hospital (BWH), a 793-bed academic medical center, received a continuously infused opioid(s) in the ICU and required mechanical ventilation for greater than or equal to 24 hours. Patients chronically using higher-dose opioids (daily opioid use ≥ 100 mg morphine milligram equivalent [MME]) or greater than or equal to 3 nonopioid analgesics on a scheduled basis prior to ICU admission, who presented with a burn injury, underwent coronary artery bypass graft (CABG) surgery, who required extracorporeal membrane oxygenation, or who received a continuous neuromuscular infusion in the ICU were excluded.

Although an ERAS protocol has been in use at BWH for more than a decade for patients admitted directly to the floor after major surgery (5), neither an ERAS protocol nor an ICU pain management protocol in use in study SICU during either study period. While many "A" for Assessment, Prevention, and Manage pain; "B" for Both Spontaneous Awakening Trials and Spontaneous Breathing Trials; "C" for Choice of Analgesia and Sedation; "D" for Delirium Assess, Prevent, and Manage; "E" for Early Mobility and Exercise; and "F" for Family Engagement and Empowerment (ABCDEF) bundle components were implemented in each SICU prior to 2017 (e.g., routine pain, sedation, and delirium assessment, a spontaneous awakening/spontaneous breathing protocol), the full ABCDEF bundle was not formally implemented during either study year (7). In 2017, IV acetaminophen was restricted at BWH to colorectal surgery patients (who are rarely admitted to the ICU) but due to the 2018 opiate shortages, its use was expanded to all postsurgical adults where acetaminophen was not able to be administered via the oral or enteral route. Liposomal bupivacaine was added to the BWH formulary in 2018.

The primary study outcome was daily ICU use of nonopioid analgesics either recommended (i.e., acetaminophen [either IV or oral], ketamine, neuropathic medications [i.e., gabapentin, pregabalin], or not recommended [i.e., lidocaine patches, nonsteroidal anti-inflammatory drugs (NSAIDs)]) by the PADIS guidelines (6). Secondary outcomes included: 1) baseline patient variables; 2) ICU use of epidural blocks, peripheral nerve blocks, and liposomal bupivacaine; 3) daily ICU opioid (both scheduled and as needed IV and oral/enteral) exposure; 4) daily ICU pain scores (both Visual Analog Scale-10 [VAS-10] and Clinical Pain Observation Tool [CPOT] scores) (6, 8); and 5) clinically important sequelae associated with opioid use: coma (Richmond Agitation-Sedation Scale score = –4 or –5) (9, 10), delirium (positive Confusion Assessment Method for the ICU) (11, 12), constipation (≥ 3 d without a spontaneous bowel movement) (13), and ICU mechanical ventilation requirements (presented as ICU days without mechanical ventilation and time from ICU admission to extubation ≥ 48 hr [6, 10]).

For each nonopioid analgesic, only data on scheduled use was collected given the authors felt "as needed" administration fell outside of the PADIS recommendations and represented a different prescribing decision on the part of the ICU physician (6). For the purposes of the study, methadone was considered an opioid but tramadol was not. All administered opioids were converted into equivalent IV MME doses (14). For the purposes of the study, moderate pain was deemed to be present during an ICU day when greater than or equal to 1 VAS-10 score was 5–6 or CPOT score was 3–4. Severe pain was deemed to be present during an ICU day when greater than or equal to 1 VAS-10 score was greater than or equal to 7 or CPOT score was greater than or equal to 5 (8, 12, 15, 16). All data were extracted from the MGB Epic (Verona, WI) electronic health record by trained research personnel.

Study outcomes were presented and compared between 2017 and 2019 study years as follows: 1) Dichotomous

variable data were presented as *n* (%) and compared using the Pearson chi-square test. 2) Continuous variable data were presented as a mean (SD) and compared with the Student *t* test if normally distributed or as a median (interquartile range) and compared using the Wilcoxon rank-sum test if non-normally distributed. 3) For each daily variable, the proportion of ICU days the patient received the medication (or had the clinical variable) was first calculated for each patient and then averaged across all patients in each group. A *p* value of less than or equal to 0.05 was deemed significant. All analyses were performed using SPSS 22.0 (IBM, Armonk, NY).

RESULTS

Among the 568 patients admitted to one of the three-study SICUs in 2017 on a continuous IV opioid infusion, 95 met all study inclusion criteria and 17 met one on more exclusion criteria. In 2019, 455 patients were admitted to one of the SICUs on a continuous IV opioid infusion, 74 met all inclusion criteria, and 17 were excluded. The 2017 ($n = 78$) and 2019 ($n = 57$) groups were similar except the 2019 group that was more likely to undergo major abdominal surgery and less likely to undergo thoracic surgery ($p = 0.02$) (**Table 1**). Overall, the patients were 63 years old and at ICU admission had a Sequential Organ Failure Assessment score of 9 (7–11), a Pao_2:Fio_2 ratio of 236 (77), and 73% required vasopressor support.

The 2019 (vs 2017) patients were more likely to receive scheduled acetaminophen (IV or oral) (84% vs 69%; $p = 0.05$), a peripheral nerve block (21% vs 5%; $p = 0.05$), and intraoperative liposomal bupivacaine (20% vs 0%;

TABLE 1.
Comparison of Baseline Factors Between 2017 and 2019 Groups[a]

Baseline Characteristic	2017 and 2019 ($n = 135$)	2017 ($n = 78$)	2019 ($n = 57$)	*p*
Age (yr)	63 (15)	62 (15)	64 (16)	0.53
Sex, male, *n* (%)	81 (60)	44 (56)	37 (65)	0.32
Race, *n* (%)				0.11
White	115 (85)	70 (90)	45 (79)	
Other	20 (15)	8 (10)	12 (21)	
Primary surgical site, *n* (%)				0.02
Abdominal/gastrointestinal	61 (45)	27 (35)	34 (60)	
Cardiac/lung	51 (38)	37 (47)	14 (25)	
Trauma/orthopedic	17 (13)	9 (12)	8 (14)	
Other	6 (4)	5 (6)	1 (2)	
Body mass index, *n* (%)	28 (8)	28 (7)	28 (8)	0.99
≥ 30	51 (38)	28 (36)	23 (40)	0.60
Sequential Organ Failure Assessment score, median (interquartile range)	9 (7–11)	9 (7–10)	9 (7–11)	0.58
Pao_2:Fio_2 ratio (mm Hg)	236 (77)	228 (79)	247 (74)	0.15
Platelets ($\times 10^9$/L)	149 (71)	152 (78)	144 (60)	0.55
Bilirubin (mg/dL)	1.3 (1.6)	1.2 (1.4)	1.4 (1.8)	0.42
Vasopressor use, *n* (%)	99 (73)	57 (73)	42 (74)	0.94
Norepinephrine equivalent dose > 0.1	41 (30)	21 (27)	20 (35)	0.31
Creatinine clearance (mL/min), mean (SD)	70 (42)	72 (37)	68 (48)	0.57
≤ 30, *n* (%)	19 (14)	10 (13)	9 (16)	0.62
Scheduled home opioid, *n* (%)	4 (3)	1 (1.3)	3 (5)	0.31
As needed home opioid, *n* (%)	20 (15)	12 (15)	8 (14)	0.83
Scheduled home nonopioid analgesic, *n* (%)	27 (20)	12 (15)	15 (26)	0.12

[a]Continuous variables are presented as mean (SD) unless otherwise stated.

p = 0.05) (**Table 2**). They were less likely to receive a lidocaine patch (33% vs 50%; p = 0.05). The use ketamine, an NSAID, or a neuropathic medication (i.e., gabapentin or pregabalin) was low and similar between the two groups. Concomitant use of greater than or equal to 2 PADIS-recommended nonopioid analgesics

TABLE 2.
Comparison of ICU Nonopioid Analgesic and Opioid Use Between 2017 and 2019[a]

Medication	2017 and 2019 (n = 135)	2017 (n = 78)	2019 (n = 57)	p
Scheduled nonopioid analgesic use				
Acetaminophen (IV or oral)				
Number of patients, *n* (%)	102 (76)	54 (69)	48 (84)	0.05
Average daily dose (mg)	2,095 (594)	1,887 (546)	2,328 (558)	< 0.01
Average proportion of ICU days administered, *n* (%)	70 (27)	67 (28)	74 (26)	0.16
Lidocaine patch				
Number of patients, *n* (%)	58 (43)	39 (50)	19 (33)	0.05
Average daily dose (mg)	1.8 (0.7)	1.7 (0.7)	2.0 (0.7)	0.14
Average proportion of ICU days administered, *n* (%)	55 (23)	59 (23)	47 (22)	0.07
Ketamine infusion				
Number of patients, *n* (%)	4 (3)	2 (3)	2 (4)	1.00
Average daily dose (mg)	5.2 (2.6)	7.1 (2.1)	3.3 (1.2)	0.26
Average proportion of ICU days administered, *n* (%)	43 (24)	55 (28)	32 (10)	0.51
Nonsteroidal anti-inflammatory drugs (celecoxib, ibuprofen, ketorolac, or naproxen)				
Number of patients, *n* (%)	6 (4)	2 (3)	4 (7)	0.24
Average proportion of ICU days administered, *n* (%)	28 (13)	31 (9)	27 (15)	0.76
Neuropathic (gabapentin or pregabalin)				
Number of patients, *n* (%)	16 (12)	7 (9)	9 (16)	0.23
Average proportion of ICU days administered, *n* (%)	55 (29)	58 (33)	52 (26)	0.68
Epidural block, *n* (%)	20 (15)	15 (19)	5 (9)	0.09
Peripheral nerve block, *n* (%)	16 (12)	4 (5)	12 (21)	0.05
Liposomal bupivacaine, *n* (%)	6 (4)	0 (0)	6 (11)	0.05
Opioid use				
Average daily IV morphine milligram equivalent opioid use, median (interquartile range)				
All (infusions, scheduled, as needed)	74 (45–104)	70 (42–99)	78 (49–109)	0.92
Scheduled (infusion or scheduled)	66 (42–96)	62 (39–97)	68 (47–95)	0.98
As needed	9 (5–15)	9 (5–14)	9 (5–17)	0.50
Continuous opioid infusion				
Number of patients, *n* (%)	135 (100)	78 (100)	57 (100)	1.00
Average proportion of ICU days administered, *n* (%)	51 (22)	54 (21)	48 (22)	0.14
Scheduled IV push opioid				
Number of patients, *n* (%)	6 (4)	2 (3)	4 (7)	0.24
Average proportion of ICU days administered, *n* (%)	12 (6)	14 (7)	11 (5)	0.68
Scheduled oral/enteral opioid				
Number of patients, *n* (%)	19 (14)	9 (12)	10 (18)	0.32
Average proportion of ICU days administered, *n* (%)	30 (27)	37 (34)	23 (15)	0.28

[a]Continuous data presented as mean (SD) unless otherwise stated.

on any given SICU day was low and not different between the 2019 (vs 2017) groups (18% vs 7%; $p = 0.14$).

Among individual nonopioid analgesic agents and routes of administration, 2019 (vs 2017) patients were more likely to receive IV acetaminophen (74% vs 1%; $p < 0.001$), consistent with the less restrictive 2018 BWH guidelines for use. However, the average proportion of ICU days acetaminophen (either IV or oral) was administered was similar between the 2 years. Given higher doses of IV (vs oral) acetaminophen doses are usually administered (1, 6), the average daily acetaminophen dose was significantly greater in 2019. For the other nonopioid analgesic, neither the average daily dose nor the proportion of SICU days it was administered over the total SICU days differed between the two groups.

Epidural blocks were used more frequently in 2017; peripheral nerve blocks and liposomal bupivacaine were each used more frequently in 2019 (Table 2). Total (median [interquartile range]) daily opioid exposure (for all IV and oral/enteral opioids, both scheduled and "as needed") in IV MME was similar between the 2019 (vs 2017) years (70 [42–99] vs 78 [49–109]; $p = 0.94$). While the number of patients who ever experienced moderate or severe pain was similar between the two groups, the 2019 (vs 2017) patients spent a greater proportion of ICU days with either moderate (35% vs 24%; $p = 0.04$) or severe (28% vs 18%; $p = 0.03$) pain (**Table 3**). Delirium occurred in more 2019 patients (54% vs 36%; $p = 0.05$). Coma, constipation, and mechanical ventilation requirements were similar between the two groups (Table 3).

DISCUSSION

Our study is the first published comparative evaluation of multimodal analgesic use in critically ill surgical adults before and after publication of the 2018 PADIS guidelines (6). Among the three nonopioid analgesics recommended in guidelines (i.e., acetaminophen, ketamine, and gabapentin/pregabalin), only acetaminophen was routinely used with per-patient acetaminophen use increasing by 20% after guideline publication. The use of lidocaine, not recommended in PADIS, decreased by one-third but was still administered to one-third of postguideline group patients. Fewer than 20% of the postguideline patients received greater than or equal to 2 PADIS-recommended nonopioid analgesics on any given SICU day.

While opioids remain the mainstay analgesic in critically ill adults after major surgery, multiple concerns exist with their use including respiratory depression, ileus/constipation, coma, delirium, hyperalgesia, and post-ICU continuation (1–4, 6). Multimodal analgesia, as recommended in the PADIS guidelines, is an important strategy to improve pain control and reduce opioid use (6). The use of neuropathic agents is the only PADIS nonopioid analgesia recommendation that is strong; the guidelines relied solely evidence from postsurgical CABG patients to make this recommendation (6). The efficacy and safety of neuropathic agents in critically ill adults after non-CABG surgery remain unclear. PADIS recommendations for acetaminophen, ketamine, lidocaine, and NSAID were all conditional (i.e., weak). A conditional recommendation requires the ICU team to consider individual patient factors during all analgesic prescribing decisions including whether the analgesic been shown to be beneficial in the specific surgical group they are caring for and whether the patient has risks for increased safety concerns (and thus precluding use).

One recent 2020 systematic review updated the 2015 evidence profile used in PADIS (6, 17). Across 33 randomized trials, the combined use of a nonopioid analgesic and an opioid (vs an opioid alone) was associated with reduced patient-reported pain scores at 24 hours (standard mean difference, –0.94; 95% CI, –1.37 to –0.50; low certainty) and decreased opioid consumption (in oral morphine equivalents over 24 hr; mean difference, 27.25 mg less; 95% CI, 19.80–34.69 mg less; low certainty). In terms of individual medications, reductions in opioid use were demonstrated with acetaminophen, ketamine, NSAIDs, and pregabalin (17). Building on a 2018 Cochrane Review of perioperative lidocaine use after major surgery (18), lidocaine has not been associated with either a reduction in pain or opioid use in critically ill surgical adults (17).

After guideline publication, the daily ICU opioid exposure remained similar between the 2 years. The fact we chose a criterion to exclude patients with regular prehospital opioid use (100 MME/d) that is higher than recommended by Centers for Disease Control criteria (50 MME/d) may have also contributed to the lack of difference in daily ICU opioid exposure between groups. The specific reason(s) for our finding that the proportion of ICU days the 2019 spent with moderate or severe pain increased from 2017 remains unclear given the

TABLE 3.
Comparison of ICU Pain, Coma, Delirium, Constipation, and Related ICU Outcomes Between 2017 and 2019

Outcome	2017 and 2019 (*n* = 135)	2017 (*n* = 78)	2019 (*n* = 57)	*p*
Moderate pain (VAS/NRS ≥ 4 or CPOT ≥ 3), *n* (%)				
Ever present for ≥ 1 d	107 (79)	58 (74)	49 (86)	0.10
Proportion of days detected once	31 (24)	27 (24)	36 (35)	0.04
Proportion of days detected ≥ twice	13 (17)	12 (17)	14 (18)	0.59
Severe pain (VAS/NRS ≥ 6 or CPOT ≥ 5), *n* (%)				
Ever present for ≥ 1 d	76 (56)	40 (51)	36 (63)	0.17
Proportion of days detected once	16 (19)	13.1 (18)	20 (26)	0.04
Proportion of days detected ≥ twice	5 (10)	4.9 (10)	6 (11)	0.60
Coma, *n* (%)				
Ever present for ≥ 1 d	95 (70)	50 (64)	45 (79)	0.06
Proportion of days with coma	16 (19)	13.1 (18)	20 (19)	0.05
Delirium, *n* (%)				
Ever present for ≥ 1 d	88 (65)	28 (36)	31 (54)	0.05
Proportion days with delirium	34 (32)	26 (29)	45 (34)	0.06
Constipation, *n* (%)				
Ever present	119 (88)	71 (91)	48 (84)	0.23
Proportion of days without a spontaneous bowel movement	82 (25)	85.3 (22)	78 (27)	0.10
Mechanical ventilation, median (interquartile range)				
ICU days spent without mechanical ventilation	3 (1–5)	3 (1–4)	3 (1–6)	0.34
Time from ICU admission to extubation ≥ 48 hr	4 (3–6)	4 (2–5)	3 (3–7)	0.54

CPOT = clinical pain observational tool, NRS = numerical rating scale, VAS = Visual Analog Scale.

retrospective nature of our study. It may be possible that nurses in 2019 were more rigorous in conducting pain evaluations, that patients were more wakeful and able to self-report pain, or were more aggressively mobilized (often associated with increased pain). Although the ABCDEF bundle was neither fully nor formally implemented in either study year, its use is associated with greater reported pain (7). The greater pain in 2019 may also be associated with the greater number of patients (compared with 2017) undergoing major abdominal surgery; abdominal procedures are associated with greater pain than cardiothoracic procedures (19).

It also remains unclear why more 2019 patients experienced delirium given baseline age and severity of illness and ICU coma, opioid exposure, and mechanical ventilation days were similar between the 2 years (6, 10, 12). However, important factors known to affect ICU delirium occurrence (e.g., blood transfusions, worsening ICU severity of illness) were not collected as part of the study (6). The fact more 2019 (vs 2017) patients received a continuous infusion of propofol and/or dexmedetomidine (not previously reported) suggests the 2019 patients may have had greater daily ICU severity of illness (6).

Our study has limitations. Its retrospective design precludes understating the physician rationale for individual analgesic prescribing. Variability in analgesic prescribing practices between the surgical intensivists who managed the patients may have existed. We relied on global pain assessments conducted by nurses and did not consider specific pain-related sources or symptoms. We assumed all analgesic therapy was titrated to maintain patients in a relatively pain-free state. The use of analgesics for nonpain-related reasons (e.g., acetaminophen for fever treatment) is not known. While patients taking higher-dose opioids prior to

surgery were excluded, patients with chronic pain syndromes or hyperalgesia may have been included (3). Our results may not apply to postsurgical patients admitted to the ICU who are not initially managed with a continuous opioid infusion or who are quickly extubated. Our results may also not apply at other centers where postoperative analgesic strategies in critically ill adults are protocolized or are different. The proportion of patients undergoing major abdominal and thoracic surgery was different between the 2 years; analgesic approaches may be different between these two populations. Last, we did not collect data on post-ICU opioid use and thus do not know if the nonopioid analgesic practices we describe influenced this outcome.

CONCLUSIONS

At our center, nonopioid analgesic prescribing patterns in surgical critically ill adults consistent with PADIS guideline recommendations appear to have changed little after their publication. Our study highlights areas for future research including the development and evaluation of strategies to implement PADIS guideline pain-related recommendations and prospective, controlled research evaluating the efficacy and efficacy of nonopioid analgesics in adults who are critically ill after major surgery.

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