New Persistent Opioid Use After Postoperative Intensive Care in US Veterans

New persistent opioid use was recently described as the most common postoperative complication after surgery in the United States. Less is known about the extent to which this problem occurs after intensive care unit (ICU) care, a setting where opioid use is common and considerable proportions of patients receive opioid prescriptions at discharge. Persistent opioid use may be a part of the post-intensive care syndrome, a syndrome of cognitive, psychiatric, and/or physical disability after treatment in an ICU.

In this study, we measure new persistent opioid use in patients discharged after postoperative intensive care within the Veterans Health Administration. We also report changes over time and values before and after 2013, when both the initiation of the Veterans Health Administration Opioid Safety Initiative (OSI) and release of pain, agitation, and delirium (PAD) guidelines for patients with critical illness occurred.

Methods | This study was approved by the institutional review board at the Durham VA Healthcare System. Deidentified data were used, obviating the need for informed consent, and analyses were aggregated. We identified a cohort of veterans who were opioid-naïve preoperatively (having had no prescriptions for any opioids for 6 months prior to admission for surgery) who received postoperative ICU care for more than 24 hours within the Veterans Health Administration between 2000 and 2016. Consistent with the recent definition, we identified new persistent use as the continuation of prescriptions for opioid-containing medications more than 3 months after discharge. We examined the annual rate of change in new persistent opioid use as well as new persistent opioid use over consecutive 3-year periods (2009-2012 and 2013-2016) around the time of OSI and the PAD guideline releases. We used generalized estimating equation models to examine changes. Analyses were performed using SAS Software, version 9.4 (SAS Institute), with significance set at $P < .05$. Data analysis occurred from October 2018 to January 2019.

Results | Of 869,193 veterans naïve to opioids who underwent surgery within the Veterans Health Administration between 2000 and 2016, 352,777 patients (40.5%) had been admitted to the ICU postoperatively for more than 24 hours. Of these, 7,729 (4.1%) developed new persistent opioid use. The demographic attributes of patients who developed new persistent opioid use vs those who did not are depicted in the Table. Patients who developed new persistent opioid use had a mean (SD) younger age (62.5 [9.0] years; 66.8 [10.0] years; $P < .001$) and had greater prevalence of alcohol use disorder (1036 of 7729 [13.4%]; 14,742 of 185,599 [7.9%]; $P < .001$) and substance use disorder (4335 of 7729 [56.1%]; 72,092 of 185,599 [38.8%]; $P < .001$).

The annual decline in adjusted odds of new persistent opioid use, 6% per year, was significant (odds ratio [OR], 0.94 [95% CI, 0.94-0.95]; $P < .001$; Figure). In the period 2013 through 2016, new persistent opioid use was 3.6% (vs 5.1% in 2009 through 2012; $P < .001$), a 39% reduction in odds (odds ratio, 0.61 [95% CI, 0.57-0.66]).

Discussion | We observed that a considerable proportion of US veterans who survived postoperative ICU stay developed new persistent opioid use. The incidence decreased significantly with time, and smaller proportions of such patients progressed to persistent opioid use from 2000 through 2016. Also, significantly fewer patients had new persistent opioid use over the 3 years after vs before the OSI and PAD guidelines were released.
Current rates of new persistent opioid use after postoperative intensive care in US veterans are high (approximately 4%), but the decreasing trends are reassuring, especially given the markedly higher rates of mental illness and chronic pain in veterans. Reasons for the observed trends are unclear, but better ICU pain management and changing opioid prescription practices in the aftermath of the OSI initiative as well as PAD guidelines are likely contributors. The emphasis on prompt delivery of mental health, substance use disorder, and social support services within the VA might also have played a role, and the feasibility of expansion of such a model to the general population needs to be investigated.

This study has limitations. We did not examine patient or ICU characteristics that may be associated with persistent opioid use, we may have not counted opioid prescriptions that were filled outside the VA system, and we did not untangle the effect of the release of PAD guidelines from the effect of the OSI guidelines.

However, this report generates descriptive evidence about this emerging public health concern. It will serve as an impetus to instigate further research into causal factors and preventive strategies.

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Patients with gastric adenocarcinoma identified on final pathology reports were identified from the US HIPEC Collaborative, a multi-institutional data set composed of more than 2300 patients from 12 academic medical centers. Institutional review board approval was obtained at each participating institution. A retrospective analysis of baseline demographic, clinicopathologic, operative, and postoperative factors was performed using descriptive statistics. Both OS and recurrence-free survival were analyzed using the Kaplan-Meier method. No informed consent was required because a waiver of informed consent was requested for this study given that it was a retrospective medical record review of data with no direct patient contact. Deidentified data were used for all distribution and analysis.

Results | Overall, 28 patients (17 [61%] female; mean [SD] age, 48.5 [14.2] years) with GC underwent HIPEC at 7 institutions between January 1, 2010, and December 31, 2017. Baseline demographic and clinicopathologic factors are given in the Table. Twenty-five patients (89%) had overt peritoneal dissemination, whereas 3 (11%) had positive cytologic findings on peritoneal washings. The median peritoneal carcinomatosis index (PCI) of those with peritoneal disease was 12 (interquartile range, 4-17). Curative-intent resection was performed in 23 patients; 5 patients underwent palliative HIPEC. In the curative-intent population, complete cytoreduction was achieved in 16 (70%) of 23 patients. Twenty-seven patients (96%) received neoadjuvant or adjuvant chemotherapy. Although chemotherapy regimens (63%) were fluorouracil based, 15 distinct regimens were observed. In the curative-intent population, median recurrence-free survival was 7 months (95% CI, 4.9-9.1 months) and OS was 10 months (95% CI, 6.5-13.5 months) (Figure, A and B). Improved median OS was observed among the 11 curative-intent patients with a PCI of 9 or less compared with the 12 patients with PCI scores greater than 9 (26 vs 8 months; P = .01). After palliative HIPEC, the median OS was only 2 months (range, 2-13 months).

Perioperative morbidity among all patients was high: 21 (75%) experienced at least 1 complication, 5 (18%) of which were Clavien-Dindo grade 3 or higher. Five patients required a subsequent operation for indications, including anastomotic leak, intra-abdominal infection, or obstruction. The need for nutritional support was common; total parenteral nutrition was required for 13 patients (46%), whereas 9 (32%) of 28 needed supplemental tube feeds. The median length of stay was 11 days (interquartile range, 8-15 days), and 7 patients (25%) required readmission. Two patients (7%) died within 90 days of surgery.

Discussion | The optimal role for HIPEC in the treatment of advanced GC remains poorly defined. Because of the lack of high-quality evidence, unclear criteria for patient selection, and biological differences among patients, no standardized approach has emerged. In addition, no clear survival advantage exists compared with results reported with standard chemotherapy alone, and little progress has been made in patient outcomes. More than a decade ago, published reviews of European and US patients undergoing CRS-HIPEC for GC reported a median OS of 8.0 to 9.2 months, with a perioperative morbidity ranging from 27.8% to 35.0%. Comparable mortality and morbidity rates from our current series suggest that outcomes remain poor, even among experienced centers. Although multiple studies indicate there may be a survival benefit among patients with lower PCI scores, a consensus cutoff has not been determined. Clear criteria to aid in patient se-