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ORIGINAL RESEARCH

Impact of Ketamine on Opioid Use and Persistent Pain After Cytoreductive Surgery with Hyperthermic Chemotherapy

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Background: Persistent pain and opioid use can be devastating after cytoreductive surgery (CRS) and hyperthermic intraoperative chemotherapy (HIPEC).

Methods: We conducted a retrospective study to investigate the impact of ketamine use on postoperative complications and persistent and chronic pain after CRS-HIPEC.

Results: Ketamine reduced perioperative opioid use before and after implementation of recovery after surgery programs. Ketamine did not impact the formation of persistent and chronic pain formation and long-term opioid use. Postoperative complications and postoperative re-operations were independent predictors of persistent pain. Interestingly, the risk of having a complication was increased by 1% for every doubling in opioids used intraoperatively.

Conclusion: Ketamine use reduces perioperative opioid consumption in patients undergoing CRS-HIPEC, but it is not associated with improvements in long-term opioid use and chronic pain.

Keywords: chronic pain, cancer, neoplasm, opioids, ketamine, surgery, cytoreductive surgery

Introduction

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is increasingly offered as a treatment option for patients with peritoneal spread of appendiceal, colorectal, peritoneal mesothelioma, gastric carcinoma, and more recently to gynecological malignancies.[1–3] CRS-HIPEC involves extensive peritoneal stripping, multi-organ resections, and the intraperitoneal administration of heated (up to 42°C) chemotherapy agents (eg, mitomycin C, cisplatin or oxaliplatin).[4]

After CRS-HIPEC, acute pain can be severe and, in many patients, difficult to treat.[5] The current perioperative management of CRS-HIPEC related pain relies on multimodal analgesia strategies using regional anesthesia and systemic analgesics, including opioids.[6,7] Unfortunately, abdominal pain may remain undertreated for some patients, and can lead to the consumption of large amounts of opioids that can be as high 1000 mg of morphine equivalent daily.[7,8] In those patients, high opioid consumption is an independent risk factor for postoperative adverse outcomes, delayed recovery and persistent postoperative opioid use.[9]

Ketamine is a N-methyl-D- aspartate receptor antagonist that at high doses has anesthetic effects but at low doses is a potent analgesic.[10] Ketamine has opioid-sparing effects and delays the time of first-time opioid dose after major surgery.[11,12]

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Clinical studies demonstrate that ketamine does not show significant clinical effects on the reduction of persistent postsurgical pain.[13,14] However, a randomized controlled trial by De Kock et al demonstrated that intravenous ketamine (0.5 mg/kg bolus followed by an infusion of 0.25 mg/kg per h) reduced analgesic use one, six and 12 months after open laparotomy.[15]

We consider important to find strategies to effectively treat pain and reduce acute and long-term exposure to opioids after CRS-HIPEC. The impact of low intraoperative doses of ketamine on acute, persistent, and chronic pain and opioid use after CRS-HIPEC is unknown. Here, we tested the hypothesis that a low dose of intravenous ketamine intraoperatively is associated with a significant reduction in opioid use perioperatively and long term after CRS-HIPEC.

Materials and Methods

This was a retrospective study approved by the Institutional Review Board (IRB) of the University of Texas MD Anderson Cancer Center (PA 14–0160). After obtaining waiver of informed consent and according to data confidentiality and compliance with the Declaration of Helsinki, we collected demographic, disease status, and perioperative data of patients 18 years of age or older who were treated with CRS-HIPEC for appendiceal malignancy between January 2006 and August 2018. We excluded patients who had CRS-HIPEC surgery for recurrent disease and those with missing data on the primary and secondary endpoints.

Our treatment variable was the use of ketamine HCl (Ketalar, Hospira Inc, Illinois, USA) intraoperatively. In our institution, ketamine entered routinely as part of the analgesic armamentarium for CRS-HIPEC in 2012 during the implementation of enhanced recovery after surgery (ERAS). Ketamine was administered intraoperatively according to the attending anaesthesiologist clinical judgment. Typically, ketamine was given as an intravenous bolus of 0.5–1 mg/kg followed by a continuous infusion of 1–5 mcg/kg/min. The primary outcome of the study was persistent pain after CRS-HIPEC. Persistent pain was defined as any abdominal pain six months after surgery. Secondary outcomes included intraoperative, inpatient postoperative opioid use, chronic pain (one year after surgery), length of stay and postoperative complications using Clavien-Dindo scale. We used morphine equivalent daily dose (MEDD) to quantify opioid consumption.

Statistical Analysis

Patients' demographics, disease status, and outcomes were summarized through descriptive statistics. Logarithmic transformation to base 2 was performed to the variables, which were not normally distributed in the original scale. Wilcoxon rank-sum tests were used to compare location parameters of continuous distributions between patient groups. Fisher's exact or Chi-square test was used to evaluate the association between two categorical variables. The multivariate logistic regression model was used to evaluate the effect of important covariates on the status of postoperative complication. All clinical important covariates were included in the full model for model selection. A backward model selection method was used and included covariates with a p-value less than 0.20. A $p < 0.05$ was considered statistically significant. We did not perform a sample size analysis because the effect size of the ketamine in this patient population is unknown. Statistical software SAS 9.4 (SAS, Cary, NC) was used for all the analyses.

Results

Overall Cohort of Patients

A total of 329 patients were included in the study. Overall, the median (range) age of the patient population was 53.8 (18–75) years old. There were more women (n=206, 62.6%) than men (n=123, 37.4%) patients, and the most common ASA physical status was 3 (85.4%). The most common tumour grade was low (n=220, 66.9%) and 94.2% (n=310) were treated with mitomycin C intraoperatively. Despite fifty-three patients not having a cytoreductive score, the most common score was 1 (67.57%). The median (range) MEDD received intraoperatively and postoperatively was 58 (0–9185) and 907.7 (0–28,307.6). Sixty-eight percent (n=223) of the patients had a complication postoperatively, and in 52 of them (15.8%) the severity was 3 or higher on the Clavien-Dindo scale.

In terms of postoperative pain, 31.1% (n=87), 12.3% (n=22) and 9.6% (n=16) of the patients were reporting pain one, six (persistent) and 12 (chronic) months after surgery. Overall, pain was mild since the median pain scores one, six and 12 months after surgery were 3, 3, and 3.5 on the verbal numerical rating scale for the patients with pain. Remarkably, 79.9% (n=231) of the patients were taking opioid one month postoperatively. The rate of opioid use diminished six (21.0%, n=53) and twelve (12.9%, n=30) months after surgery.

In 2012, we started our ERAS in CRS-HIPEC patients. One of the goals of ERAS programs is to reduce opioids perioperatively; therefore, we conducted a subanalysis in patients who received (or not) ketamine after 2012. The subanalysis included 224 patients, of whom 99 subjects received ketamine, and 125 did not receive (Table 1). Those in the ketamine group were slightly younger and more likely to have an ASA 1–2. Other demographic and tumour-related variables were not statistically significant.

One month after surgery, 79% (n=253) of the patients were taking opioids (n=40 missing data). Among the 253 patients with information (76 with missing data) on opioid use six months postoperatively, 53 of them were taking opioids (20.95%). Lastly, one year after surgery, 12.93% (n=30 out of 202) of the patients were taking opioids one year after surgery.

Association Between Ketamine and Opioid Consumption

About a third of the patients (n=99, 30.1%) received ketamine intraoperatively. As shown in Table 1, patients who received ketamine had significantly lower low tumour grades, had a higher rate of neoadjuvant therapy administration and underwent long surgical procedures. The analysis demonstrated that opioid consumption intraoperatively and during admission to the nursing ward was significantly lower in patients who received ketamine (Table 2). Briefly, patients treated with ketamine had a nearly 7-fold decrease in the median use of opioids intraoperatively and received more than 200 MEDD less than those who did not receive ketamine.

After ERAS, the analysis showed that ketamine-treated subjects had a statistically significant lower consumption of intravenous opioids in morphine equivalents (median [range]: 15 [0–111] mg than those not receiving the analgesic (44, [0–260], Table 2). While the postoperative opioid consumption was also lower in the ketamine group (751.2, [9.3–5928]) than in the no ketamine group (813.1, [0–8,727.4]), and the difference was not statistically significant (p=0.085). The rate of opioid use one, six, and twelve months after surgery were not significantly different between the groups (Table 3).

Association Between Ketamine, Persistent and Chronic Pain

Overall, ketamine was not significantly associated with lower pain scores one, six, and twelve months after surgery.

Table 1 Demographic Characteristics

Variable		All Patients (n=329)			Post-ERAS (n=224)		
		Ketamine No	Ketamine Yes	p- value	Ketamine No	Ketamine Yes	p- value
Age, years	Median (Range)	53.93 (23.2–74.2)	53.69 (17.7–75.0)	0.430	58.18 (23.2–74.2)	53.69 (17.7–75.0)	0.008
BMI	Median (Range)	27.25 (16.2–48.9)	27.05 (17.6–51.5)	0.842	27.13 (16.2–48.4)	27.05 (17.6–51.5)	0.770
Gender	Female Male	141 (61.3%) 89 (38.7%)	65 (65.7%) 34 (34.3%)	0.454	74 (59.2%) 51 (40.8%)	65 (65.7%) 34 (34.3%)	0.323
ASA physical Status	1/2 3/4	35 (15.2%) 195 (84.8%)	10 (10.1%) 89 (89.9%)	0.215	4 (3.2%) 121 (96.8%)	10 (10.1%) 89 (89.9%)	0.050
Neoadjuvant Chemotherapy	0 1	168 (73%) 62 (27%)	62 (62.6%) 37 (37.4%)	0.059	80 (64%) 45 (36%)	62 (62.6%) 37 (37.4%)	0.832
Cigarette Smoking	No Yes	226 (98.3%) 4 (1.7%)	96 (97%) 3 (3%)	0.434	123 (98.4%) 2 (1.6%)	96 (97%) 3 (3%)	0.657
Tumor Grade	High Intermediate Low	29 (12.6%) 38 (16.5%) 163 (70.9%)	14 (14.1%) 28 (28.3%) 57 (57.6%)	0.035	24 (19.2%) 31 (24.8%) 70 (56%)	14 (14.1%) 28 (28.3%) 57 (57.6%)	0.574
Chemotherapy Perfusion type	Cis/Oxaliplatin Mitomycin	11 (4.8%) 219 (95.2%)	8 (8.1%) 91 (91.9%)	0.240	9 (7.2%) 116 (92.8%)	8 (8.1%) 91 (91.9%)	0.805
Peritoneal carcinomatosis index	Median (Range)	17 (2–39)	15 (2–39)	0.177	18 (2–39)	15 (2–39)	0.188
Anest duration (min)	Median (Range)	622 (331–1101)	555 (379–1019	0.007	628.14 (148.82)	599.59 (144.15)	0.080

Abbreviations: BMI, body mass index; ASA, American society of Anesthesiologists; Cis, cisplatin; Anest, anesthesia; Min, minutes.

Table 2 Effect of Perioperative Opioid Use, Length of Stay and Complications

		All Patients (n=329)			Post-ERAS (n=224)		
		Ketamine No	Ketamine Yes	P value	Ketamine No	Ketamine Yes	P value
Intraoperative opioid use, mg (morphine equivalents)		101.25 (0–9185)	15 (0–111)	<0.001	44 (0–260)	15 (0–111)	<0.0001
Postoperative opioid use, mg (morphine equivalents)		977.7 (40–28,307.6)	751.2 (9.3–5928)	0.004	813.1 (0–8.727.4)	751.2 (9.3–5.928.0)	0.085
Length of stay (days)		15.5 (5–113)	10 (6–68)	<0.0001	12 (5~72)	10 (6~68)	0.009
Postoperative complications	No	63 (27.4%)	43 (43.4%)	0.0043	43 (34.4%)	43 (43.4%)	0.167
	Yes	167 (72.6%)	56 (56.6%)		82 (65.6%)	56 (56.6%)	

Table 3 Effect of Ketamine on Persistent and Chronic Pain and Opioid Use

		All Patients (n=329)			Post-ERAS (n=224)		
		One Month Postoperatively					
		Ketamine No	Ketamine Yes	P value	Ketamine No	Ketamine Yes	P value
Any opioid Use	No Yes	38 (19%) 162 (81%)	20 (22.5%) 69 (77.5%)	0.496	23 (19.7%) 94 (80.3%)	20 (22.5%) 69 (77.5%)	0.623
Any pain	No Yes	136 (69.4%) 60 (30.6%)	57 (67.9%) 27 (32.1%)	0.800	75 (65.8%) 39 (34.2%)	57 (67.9%) 27 (32.1%)	0.760
Pain (0–10)		0 (0–9)	0 (0–8)	0.795	0 (0–9)	0 (0–8)	0.358
Six Months Postoperatively							
Any opioid Use	No Yes	143 (79.9%) 36 (20.1%)	57 (77%) 17 (23%)	0.611	75 (77.3%) 22 (22.7%)	57 (77%) 17 (23%)	0.964
Any pain	No Yes	106 (89.1%) 13 (10.9%)	51 (85%) 9 (15%)	0.433	68 (88.3%) 9 (11.7%)	51 (85%) 9 (15%)	0.569
Pain (0–10)		0 (0–7)	0 (0–5)	0.442	0 (0–7)	0 (0–5)	0.584
Twelve Months Postoperatively							
Opioid	No Yes	147 (88%) 20 (12%)	55 (84.6%) 10 (15.4%)	0.4871	78 (85.7%) 13 (14.3%)	55 (84.6%) 10 (15.4%)	0.849
Any pain Use	No Yes	102 (87.9%) 14 (12.1%)	48 (96%) 2 (4%)	0.152	53 (84.1%) 10 (15.9%)	48 (96%) 2 (4%)	0.063
Pain (0–10)		0 (0–10)	0 (0–4)	0.113	0 (0–10)	0 (0–4)	0.045

Also, we investigated the impact of ketamine on persistent and chronic pain in patients who were part of our ERAS program. The proportion of patients complaining of pain and the pain severity one and six months after surgery was similar between patients treated with and without ketamine. Notably, the median [range] severity of pain 12 months after surgery was lower in those treated with ketamine (0: [0–4]) than in patients who did not receive the drug (0 [0–10]), p=0.045). Since new surgeries occurring within the year of the CRS-HIPEC procedure could influence opioid intake and the presence of chronic, we investigated the rate of re-operations in both groups of patients. The data indicate that there were no significant differences in the rates of re-operations six and 12 months after the CRS-HIPEC surgery

for both groups of patients (Table 3). We used a multivariate logistic regression model to evaluate the effect of covariates on pain at six months. We observed that the presence of any postoperative complications (odds ratio, OR; 95% confidence interval, CI: 5.4, 1.53–18.99, p=0.008) and postoperative re-operations (OR, 95% CI: 19.45, 1.63–232.16, p=0.01) were independent predictors of persistent pain.

Association Between Ketamine, Length of Stay and Postoperative Complications

Opioids are associated with postoperative complications and increased length of stay. Our data indicate that ketamine has opioid-sparing effects. Therefore, we investigated whether ketamine was associated with a reduction in postoperative complications and shorter length of stay in our cohort of patients. The statistical analysis demonstrated that patients treated with ketamine (10 [6–68] days) stayed 5 days less in the hospital than those who did not receive this drug (15.5 [5–113] days), p<0.001, Table 2). Remarkably, patients in the ketamine group had also fewer postoperative complications (n=56, 56.6%) than those in the non-ketamine group (n=167, 72.6%, p=0.004). However, this observation was not statistically significant in the ERAS cohort of patients (Table 2).

The multivariate logistic regression model used to evaluate the effect of covariates on postoperative complications after implementation of ERAS demonstrated that the duration of anaesthesia (OR, 95% CI: 1.004, 1.002–1.006, p < 0.001) and mitomycin use (OR, 95% CI: 3.29, 1.86–0.96, p = 0.035) were independent risk factors. While ketamine was not an independent risk factor associated with a reduction in postoperative complications, the odds of having a postoperative complication were increased by 1% for every doubling in MEDD used intraoperatively (OR, 95% CI: 1.1, 1.03–1.17, p=0.004).

Discussion

This retrospective study suggests that intravenous ketamine can significantly reduce opioids perioperatively when given during CRS-HIPEC surgery but does not decrease the formation of persistent and chronic pain. In support of this finding, different studies indicate that ketamine has opioid-sparing effects when it is administered during major surgery.[16,17] For instance, intravenous ketamine was associated with a reduction of approximately 50 mg of morphine equivalents during cardiac surgery, which is similar to the decrease of 47 mg found in our study.[16] Our work also shows that patients treated with ketamine required less opioids postoperatively. While the reduction in the median opioid use (226.5 mg morphine equivalents) was statistically significant when we included patients before ERAS, the observed difference in ERAS patients did not reach statistical significance. The current evidence indicates that ketamine has opioid-sparing effects in the postoperative period. For instance, a recent meta-analysis that included 8431 patients from 130 studies demonstrated intravenous ketamine was associated with a 24- and 48-hours reduction in opioids of 8 mg and 13 mg, respectively.[18] Therefore, we consider that a median reduction of 62 mg of morphine equivalents is clinically relevant.

High dosages of opioids can slow the postoperative recovery of patients since they are associated with postoperative complications.[19] Ketamine has well-documented postoperative opioid-sparing effects.[20,21] Here, we demonstrate that ketamine was associated with a statistically significant reduction in postoperative complications when we included patients outside ERAS pathways (before 2012). However, the effect on complications was not observed when the analysis was restricted to patients who had surgery after the year 2012, suggesting that the substantial reduction in opioid use associated with ketamine is more impactful in patients outside ERAS pathways. However, it is worth considering that our analysis could have been underpowered to demonstrate a significant effect in patients post ERAS implementation, since we observed a 9% reduction in complications between patients who were treated and not treated with ketamine.

Persistent and chronic postsurgical pain is a debilitating complication of major abdominal surgery.[22] Here, we report that 12.3% and 9.6% of the patients reported pain at six and 12 months after surgery. These incidences are similar to those reported in two different studies that included a mixed surgical population of patients.[23,24] In our cohort of patients, re-operations and postoperative complications were associated with persistent postoperative pain. It has been theorized that ketamine could reduce the incidence of postsurgical persistent and chronic pain.[25] Chaparro et al recently demonstrated in a systematic review that intravenous ketamine in comparison to placebo significantly reduced by 50% the risk of persistent pain six months postoperatively.[26] However, most recent evidence contradicts Chaparro's findings.[27] Here, we could not demonstrate a significant difference in chronic pain after CRS-HIPEC surgery between those treated with and without ketamine. However, our analysis showed that 15.9% of the patients not receiving ketamine complained of chronic pain (at 12 months) in comparison to 4% in the

ketamine group, suggesting a possible protective effect. The lack of strong association between the use of ketamine and postoperative persistent and chronic pain in our patient population can be explained by the fact that new surgical trauma due to postoperative complications is an independent risk factor for chronic pain and those patients with re-operations might not have received ketamine during their redo-surgeries.

We also investigated whether ketamine was associated with a reduction in long-term opioid use since patients with chronic pain might receive these analgesics as part of their analgesic treatment. Our study demonstrated that ketamine was not associated with a decrease in the incidence of persistent and chronic opioid use. Our findings agree with previous studies.[28–30] For instance, in a study by Nielsen et al ketamine did not reduce persistent opioid (six months) use after spine surgery.[28] Similarly, a randomized controlled trial conducted by Chumbley et al showed that ketamine did not cause a reduction in opioid use six and 12 months after thoracic surgery.[29]

Our study has significant limitations. First, this was a retrospective study. Unknown factors can influence (confounding) the findings of our analysis (ie, preoperative exposure to opioids). The long duration of observation, over which multiple factors were likely to be changing can further confound our results. We tried to adjust for such changes in practice by dividing the period of observation in those before and after ERAS implementation. Second, the duration of the infusion of ketamine was limited to the intraoperative period. Extending the duration of the administration of ketamine might have been associated with a reduction in the transition from acute to persistent to chronic pain. Third, the presence of persistent and chronic pain and its intensity were retrospectively collected from electronic medical records; thus, the rates presented here might have been underestimated. Last, we could not quantify opioid consumption sixth and 12 months of surgery. Therefore, our study did not address any potential long-term opioid-sparing effect of ketamine. This is a retrospective study of a single centre; therefore, the generalizability of the results is limited to the population of patients included in this work, and our findings should be considered carefully.

In conclusion, the infusion of ketamine intravenously during CRS-HIPEC is associated with short-term opioid-sparing effects but does not have significant effects on postoperative persistent and chronic opioid use and pain. The results of the present study need to be validated in a randomized controlled trial.

Author Contributions

All authors made a significant contribution to the work reported, in the conception, study design, execution, acquisition of data, analysis and interpretation and gave final approval of the version to be published. All authors have agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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