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Contents

Chronic postsurgical pain after ambulatory surgeries: a prospective cohort study

Submission ID

21

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INTRODUCTION

Chronic postsurgical pain (CPSP) is a recognized complication after various surgical procedures, with an incidence ranging from 5% to 50%.[1] Patients having outpatient surgery may experience significant postdischarge pain, as noted by a systematic review in which only 42% of studies evaluated postdischarge pain and reported an overall incidence of approximately 45%.[2] Most of these studies had a short follow-up period of 24 hr to 7 days. Hence, there is a need to evaluate the incidence of CPSP after outpatient surgeries and elucidate factors associated with it.[3] Our primary objective was to determine the incidence of CPSP. Secondarily we assessed the intensity of CPSP, incidence of moderate-to-severe CPSP, and explored the factors associated with it.

METHODS

This is a prospective cohort study of adult patients having outpatient surgeries with a potential to cause moderate-to-severe postoperative pain, such as cholecystectomy, appendectomy, ovarian cystectomy, and hernia repair. Patients having a nerve block or neuraxial analgesia were excluded. Preoperatively we collected anxiety and depression scores (Hospital Anxiety and Depression Scale); pain catastrophizing (Pain Catastrophizing Scale); presence and intensity of preoperative pain (mild/moderate/severe) within the surgical area; and presence of chronic pain in other body parts. All patients had general anesthetic and participated in a previous randomized controlled trial (RCT) comparing morphine or hydromorphone used in recovery unit and showed no difference in the rate of achieving satisfactory analgesia, defined as pain intensity of < 4/10 (0–10 numerical rating scale [NRS]).[4] Patients were followed up by a phone call after 24 hr and study outcomes were collected at three months by a mailed package with prepaid envelopes or by a backup phone call. Incidences of CPSP were reported as rate (%) with

95% confidence interval (CI), and intensity using a 0–10 NRS (95% CI). We used logistic regression to explore factors associated with CPSP adjusting for baseline catastrophizing and depression.

RESULTS

Among 402 RCT patients, 208 completed our 3-month follow-up and were included in the analysis. Included patients mostly had cholecystectomy (33%), inguinal hernia repair (22%), and gynecological surgeries (e.g., ovarian cystectomy, salpingectomy, or salpingo-oophorectomy [26%]). Majority (197 [95%]) were laparoscopic. Incidence of CPSP was 18.8% (39/208), 95% CI 13.7–24.7%, with the mean (95% CI) intensity being 5.5 (4.7–6.4). Seventy-eight percent (28/39) reported having moderate-to-severe CPSP. Rates of CPSP with cholecystectomy (21%) and inguinal hernia (22%) repair were similar. At baseline (Figure), patients reporting CPSP had higher anxiety (median, interquartile range [IQR], 8 [4–10]; $P = 0.04$); depression (3 [1–5]; $P = 0.01$); and catastrophizing scores (12 [5–21]; $P = 0.04$). Nevertheless, none of them were significant in an adjusted model. Every unit increase in pain over the first 24 hr was significantly associated with increased odds of moderate-to-severe CPSP at three months; odds ratio, 1.28; 95% CI, 1.04 to 1.58 (Figure).

DISCUSSION

In our cohort study of 208 patients having outpatient surgery, nearly one-fifth (19%) patients reported to have CPSP at three months and more than two-thirds (72%) of them had moderate-to-severe pain. Although higher anxiety, depression, and catastrophizing preoperatively were associated with CPSP in univariate analyses, adjusted analysis did not show such association. Nevertheless, higher postoperative pain score over the first 24 hr indicated a higher risk of moderate-to-severe CPSP. As there are no formal care pathways to address the need to prevent CPSP after outpatient surgeries, studies need to focus on feasible strategies to provide continuing care.[5]

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Figure Baseline characteristics and regression analysis of predictive factors

Baseline characteristics between patients with and without CPSP at 3 months					
Baseline characteristics		**Total (n=208)**	**CPSP absent (n=169)**	**CPSP present (n=39)**	***P* Value**
Age, years, mean (SD)		48.4 (13.8)	49.2 (13.4)	44.8 (15.1)	.07
Female sex, n (%)		134 (64.4)	109 (64.5)	25 (64.1)	.96
Anxiety score, median (IQR)		6 (3–9)	5 (3–9)	8 (4–10)	.04
Depression score, median (IQR)		2 (1–4)	1 (0–4)	3 (1–5)	.01
Catastrophizing score, median (IQR)		9 (2–16)	9 (2–15)	12 (5–21)	.04
Preoperative pain in the area of surgery, n (%)		85 (40.9)	65 (38.5)	20 (51.3)	.14
Moderate-to-severe preoperative pain, n (%)		42 (20.2)	32 (18.9)	10 (25.6)	.38
Chronic pain in other parts, n (%)		30 (14.4)	20 (11.8)	10 (25.6)	.03
Chronic moderate-to-severe pain, n (%)		13 (6.3)	9 (5.3)	4 (10.3)	.27
Type of surgery, n (%)	Laparoscopic	197 (94.7)	158 (93.5)	39 (100.0)	.22
	Open	11 (5.3)	11 (6.5)	0 (0.0)	–
Duration of surgery, min, median (IQR)		53.0 (35.5–76.0)	53.0 (35.0–75.0)	53.0 (39.0–79.0)	.50
Highest pain in PACU, median (IQR)		5 (4–7)	5 (4–7)	7 (5–7)	.06
Highest pain in DSU, median (IQR)		3 (2–4)	3 (2–4)	4 (2–5)	.20
Average pain score over the last 24 hours, median (IQR)		4 (2–5)	4 (2–5)	5 (4–6)	.02

Adjusted association of patient factors with CPSP and moderate-to-severe CPSP				
	Any CPSP		**Moderate to severe CPSP**	
Factors	**OR (95%CI)**	**P Value**	**OR (95%CI)**	**P Value**
Depression score	1.07 (0.94–1.21)	0.30	1.14 (1.00–1.31)	0.06
Pain catastrophizing score	1.03 (0.99–1.07)	0.15	1.01 (0.96–1.05)	0.72
Average pain score during the first 24 hours	1.19 (0.99–1.42)	0.06	1.28 (1.04–1.58)	0.02

*Every one-unit increase. CI, confidence interval; CPSP, chronic postsurgical pain; DSU, day surgery unit; IQR, interquartile range; OR, odds ratio; PACU, post-anesthetic care unit; SD, standard deviation

Frailty and decisional regret after elective noncardiac surgery: a multicentre prospective cohort study

Submission ID

71

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INTRODUCTION

Frailty is a multidimensional state that results from the accumulation of age and disease-related deficits.[1] Preoperative frailty increases the likelihood of postoperative mortality by more than 2-fold and postoperative loss of independence by nearly 5-fold.[2] Decisional regret is "a negative, cognitively-based emotion that we experience when realizing or imagining that our present situation would have been better had we acted differently."[3] In health care, regret can occur following a treatment decision.[4] Patients with surgical diagnoses face a difficult choice between invasive treatments with relatively high short-term risks (e.g., having surgery) *vs* more conservative options with uncertain longer term risks (e.g., medical management or watchful waiting). After surgery, experiencing a postoperative complication is regularly cited as a predictor of decisional regret.[5] Despite the strong association between frailty and increased risk of postoperative adverse events,[2] the association between frailty and decisional regret in patients who have undergone elective noncardiac surgery remains largely unaddressed.

METHODS

Research ethics was obtained prior to conduct of this secondary analysis of a prospective, multicenter cohort study of adults ≥ 65 yr who underwent elective, inpatient noncardiac surgery. A protocol was prespecified and registered. Frailty assessments were conducted by trained research assistants or the primary investigator. The presence of frailty was classified using a Clinical Frailty Scale (CFS) score of ≥ 4. Decisional regret about undergoing surgery was collected after surgery in-person or by phone at 30, 90, and 365 days (primary ascertainment point). Decisional regret was measured on a 3-point ordinal scale (no, unsure, yes).

Unadjusted and adjusted associations of frailty and decisional regret were estimated as odds ratios (OR) and 95% credible intervals (CrI), along with estimating the probability of a nonnull association (*P* [OR > 1]), using Bayesian ordinal logistic regression under weakly information priors. Best practices in Bayesian workflows were followed. Prespecified primary

adjusted analysis were conditional on age, sex, surgical specialty, and risk of depression or anxiety. Sensitivity analysis additionally adjusted for the baseline number of comorbidities and disability score. Effect modification of frailty by surgery type was evaluated. In addition to binary frailty status, we also tested the association of different frailty levels with decisional regret risk.

RESULTS

We included 669 patients having elective, noncardiac surgery; 293 (43.8%) lived with preoperative frailty. Mean age was 73 (SD 6) yr, 317 (47.9%) were female, and 325 (48.6%) underwent orthopedic surgery. The unadjusted OR for decisional regret at 365 days in patients with frailty compared with those without was 2.21 (95% CrI, 0.98 to 5.09; *P* [OR > 1] = 0.97), and after adjustment OR = 1.68 (95% CrI, 0.84 to 3.36; *P* [OR > 1] = 0.93). Results were similar in direction and strength or association at 30 and 90 days.

Sensitivity analysis additionally adjusting for comorbidities and disabilities estimated the frailty-decisional regret association as OR = 0.89 (95% CrI, 0.37 to 2.12; *P* [OR > 1] = 0.39). There was strong evidence of effect modification by surgery type (nonorthopedic, OR = 1.90; OR (95% CrI, 1.00 to 3.59; *P* [OR > 1] = 0.98); orthopedic, OR = 0.87 (95% CrI, 0.41 to 1.91; *P* [OR > 1] = 0.36). There was also evidence of greater decisional regret at higher CFS scores than lower (CFS ≥ 5; OR = 2.06 (95% CrI, 0.81 to 5.43; *P* [OR > 1] = 0.94; CFS, 4; OR = 1.61 (95% CrI, 0.61 to 4.33; *P* [OR > 1] = 0.83).

DISCUSSION

We found moderate strength evidence that frailty was associated with greater decisional regret (93% adjusted probability of any association). Sensitivity analyses suggested complexity in this association. We found that adjustment for co-existing comorbidity and baseline disability, which are intricately linked to frailty, almost entirely attenuated the frailty-decisional regret association. In addition, we found a high probability that decisional regret was greater in those with frailty having nonorthopedic procedures, and some evidence that decisional regret with frailty was lower in orthopedic surgeries. Results highlight the need for careful, individualized discussions of the risks and benefits of surgery amongst patients with frailty.

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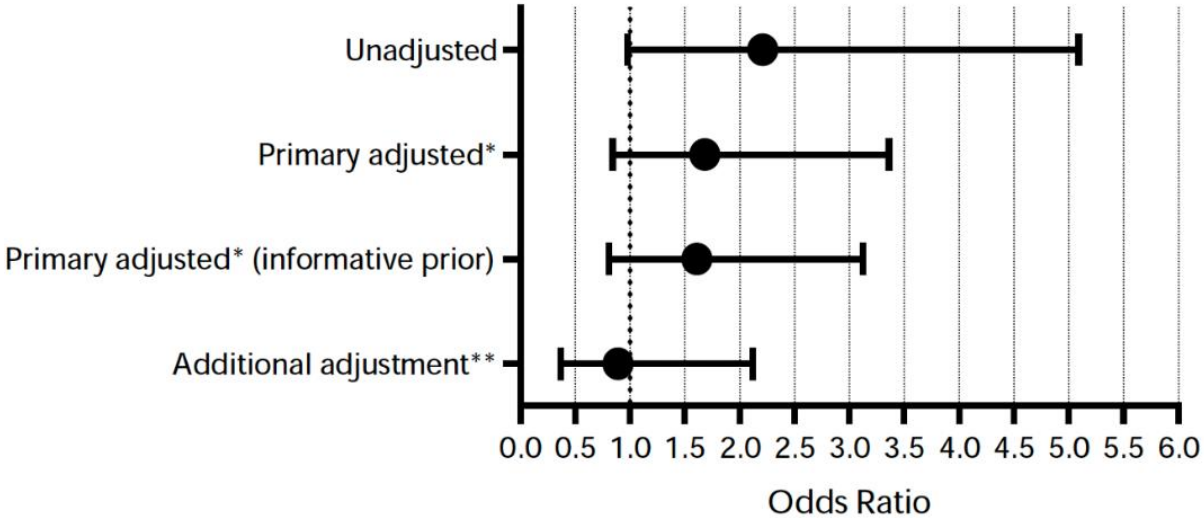
Figure Unadjusted and adjusted association of frailty with decisional regret severity one year after surgery



Data are presented as generalized odds ratio and 95% credible intervals
*Primary adjustment: age, sex, depression or anxiety, surgery type
**Additional adjustment: primary adjustment plus baseline comorbidity count and disability score
*Primary analyses used weakly informative prior distributions (normal distribution, mean = 0, SD = 1)
Informative prior distribution was a normal distribution with 95% of probability mass between an odds ratio of 1.28 to 3.28, centred at a mean of 2.0

Identifying relative efficacy of components of prehabilitation in adult surgical patients: preliminary results

Submission ID

107

AUTHORS

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INTRODUCTION

Over 500,000 Canadians undergo major surgery annually.[1] While most patients benefit from surgery, complications (20%),[2] new disability (10–20%),[3] and impaired functional recovery (50%)[4] are common. This is partly due to surgical stress, which is akin to running a marathon. Much like a runner training for a race, surgical patients can prepare for surgery through prehabilitation (a complex, multicomponent intervention comprised of one or more of preoperative exercise, nutrition, cognitive, or psychosocial interventions) to build reserve and improve postoperative recovery. Though promising, an umbrella review of 55 systematic reviews conducted by our team found that existing evidence supporting the efficacy of prehabilitation is low to very low certainty.[5] The two major issues are: heterogeneity in multicomponent prehabilitation interventions and poor review quality. As such, we sought to conduct a high-quality systematic review and component network meta-analysis (CNMA) to estimate the relative efficacy of different prehabilitation intervention components.

METHODS

Ethical review was not required for this systematic review and CNMA, which was conducted according to Cochrane collaboration recommendations. Using a PRESS-reviewed search strategy, we completed duplicate review of citations identified in Medline, Embase, CINAHL, PsychINFO, Web of Science, and the Cochrane Database (inception–February 2023). We included randomized controlled trials (RCTs) addressing a population of adults (≥ 18 yr) undergoing elective surgery where patients were exposed to a prehabilitation intervention for ≥ 7 days before surgery, compared with standard care or other prehabilitation interventions, and which reported ≥ 1 critical outcomes (complications, length of stay [LoS], physical recovery, patient-reported recovery), identified using integrated knowledge translation methods with patient partners and other knowledge users. Risk of bias assessment was performed. As prehabilitation trials test both uni- and multicomponent interventions, we used additive CNMA

models (which assumes that the total effect of an intervention will be equal to the sum of the relative component effects) to estimate the relative efficacy of pre-specified prehabilitation components (exercise, nutrition, cognitive, psychosocial) in improving critical outcomes, along with *P* scores to estimate the probability that a given intervention component was most efficacious. A full NMA model was also estimated to investigate whether evidence of interaction between prehabilitation components was present.

RESULTS

Review of 5,518 citations yielded 1,013 articles for full text review, and final inclusion of 329 unique RCTs. The median (range) sample size was *n* = 56 (10–668); oncologic, orthopedic, and major nononcologic surgical populations were most common. Complications were reported in 104 RCTs (*n* = 8,343). Unimodal nutrition and exercise were the most common components; exercise+nutrition+psychosocial was the most common multicomponent intervention. Exercise was the component with the highest efficacy (OR, 0.57; 95% confidence interval [CI], 0.45 to 0.72); nutrition also had significant efficacy (OR, 0.70; 95% CI, 0.56 to 0.86). Length of stay was reported in 113 RCTs (*n* = 9,258). Unimodal exercise and nutrition were the most common components; exercise+nutrition+psychosocial was the most common multicomponent intervention. Exercise (MD, –0.9 days; 95% CI, –1.2 to –0.5) and nutrition (MD, –0.7 days; 95% CI, –1.2 to –0.2) were similarly efficacious. Considering possible component interactions, exercise and exercise+nutrition had the highest probability of efficacy (complications), and for LoS, exercise+psychosocial or psychosocial.

DISCUSSION

Preliminary analyses conducted to estimate what prehabilitation components, or combinations of components, reduce complications and LoS with greatest efficacy suggest that exercise and nutrition provide large effect sizes in RCTs of adult surgical patients. In aiming to reduce length of stay, the role of psychosocial preparation alone, or in combination with exercise, should also be strongly considered. These results inform current prehabilitation practice and implementation, as well as design of enhanced prehabilitation interventions most likely to show efficacy in future trials. Updating of our search and analysis of patient-reported and physical recovery outcomes is ongoing.

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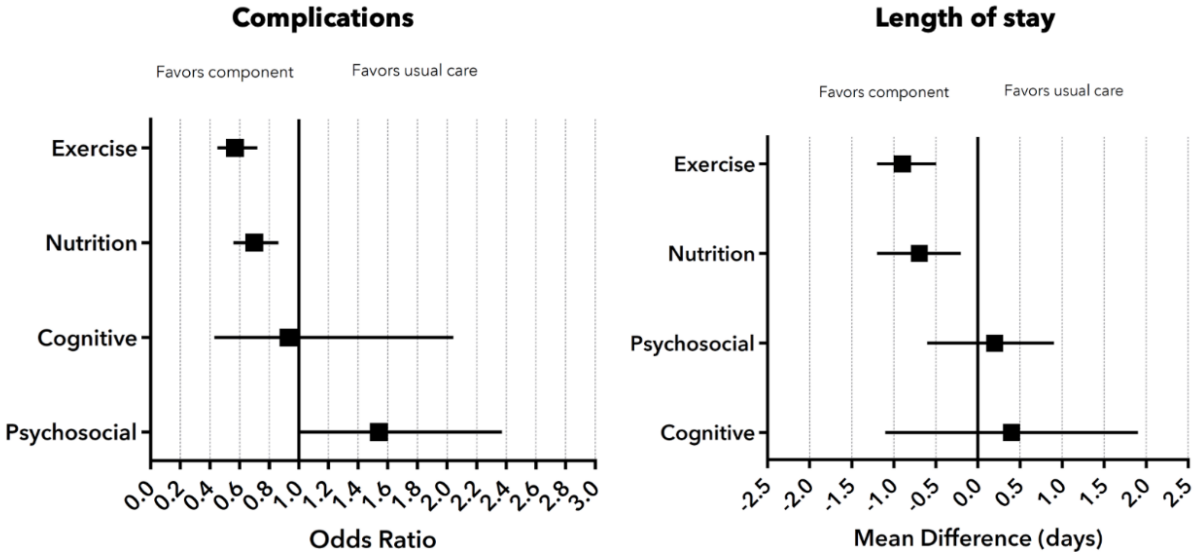
Figure Forest plots of the relative efficacy of prehabilitation components for reducing complications (left panel) and length of stay (right panel)



Estimates represent odds ratios (complications) and mean difference in days (length of stay), along with 95% CIs compared to usual or standard care. Results were estimated from an additive component network meta-analysis model, allowing information to be pooled across all comparators in the network.

Impact of short-term spinal cord stimulation for refractory neuropathic pain on sleep health parameters

Submission ID

119

AUTHORS

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INTRODUCTION

Neuropathic pain, which can often be refractory to treatment, is estimated to affect approximately 7–18 % of the population.[1] Sleep disturbances are a common comorbidity of the condition, with pain often worsening during the night. In addition, there is a bidirectional relationship between worsening pain and poor sleep, with each adversely affecting the other.[2,3] While previous research shows a beneficial effect of spinal cord stimulation (SCS) on sleep quality, its effect on various sleep health domains has not been shown via actigraphy. Our study aims to investigate the effects of short-term spinal cord stimulation on sleep health in individuals with refractory neuropathic pain using raw-data based actigraphy.

METHODS

Following institutional research ethics board (REB) approval, adult patients 18–80 yr of age with chronic, refractory neuropathic pain were enrolled after written, informed consent. Participants underwent an SCS trial with 96 hr of paresthesia-based SCS followed by equal periods of paresthesia-free SCS and placebo. Participants wore an actigraphy device (GENEActiv®, Activeinsights, Cambridge, UK) through the duration of the trial to study the effects on SCS on sleep. Sleep metrics were derived from the raw actigraphy data and included total sleep time (TST), wake after sleep onset (WASO) and sleep efficiency (SE). Actigraphy data from the preprocedure period was compared with data from day 12 after SCS insertion. The SCS was determined to be successful if there was a > 50 % reduction in numerical rating scale (NRS) scores for pain with SCS. Univariate analyses were run to determine whether the sleep metrics were different between successful (responders) and unsuccessful (nonresponders) trials. Following SCS implantation, actigraphy data was subjected to paired *t* tests within each group (responders and nonresponders), comparing it to pre-intervention baseline parameters.

RESULTS

Out of the 149 participants who were enrolled, 111 were found to have valid actigraphy data. There were no significant differences in demographic characteristics between responders and nonresponders. Univariate analysis did not reveal significant differences between participants with successful and unsuccessful trials. In participants with successful trials, TST (6.91 ± 2.09 *vs* 5.80 ± 2.22; $P < 0.001$) and WASO (1.11 ± 1.29 *vs* 0.94 ± 1.35; $P = 0.046$) showed significant reductions. Similar reductions of smaller magnitude were also found in nonresponders, but these were not statistically significant. No difference was found in SE before and after the trial.

DISCUSSION

Our results show that a successful SCS trail significantly improves sleep of individuals with refractory neuropathic pain, as evidenced by a reduction in WASO. These results are consistent with results in other studies that have examined this relationship using actigraphy. Future studies should be designed to look at longitudinal patterns and long-term impact on sleep health, pain, and quality of life.

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Table Within-group sleep parameters before and after SCS trial in responders and nonresponders

	Before SCS trial	After SCS trial	P value
Responders (n=83)			
Patient reported			
ODI score (0-100)	24.70±8.58	20.98±7.32	<0.001
PSQ3 score	182.80±78.72	146.89±90.45	0.005
PDI score	43.62±39.74	39.74±14.89	0.022
TST (hr)	7.34±2.34	6.13	<0.001
SE (%)	85.09±7.89	85.69±8.54	0.584
WASO (hr)	1.27±0.82	1.04±0.73	0.053
GENEActive data			
Total sleep time (hr)	6.91±2.09	5.80±2.22	<0.001
Sleep efficiency (%)	86.96±11.76	87.06±12.74	0.914
WASO (hr)	1.11±1.29	0.94±1.35	0.046
Physical activity-MVPA (min)	53.71±69.84	57.69±50.69	0.615
Non responders (n=28)			
Patient reported			
ODI score (0-100)	26.05±8.27	24.57±6.40	0.442
PSQ3 score	184.44±93.21	145.33±90.20	0.064
PDI score (0-70)	45.00±12.25	45.17±11.03	0.935
TST (hr)	7.65±2.26	6.55±1.81	0.029
SE (%)	86.27±6.92	86.30±7.10	0.985
WASO (hr)	1.24±0.70	1.08±0.64	0.358
GENEActive data			
Total sleep time (hr)	6.73±2.62	6.04±3.39	0.423
Sleep efficiency (%)	87.14±11.66	89.46±9.00	0.471
WASO (hr)	0.99±0.88	0.62±0.49	0.98
Physical activity -MVPA (min)	69.39±87.22	54.15±40.76	0.423

MVPA = moderate to vigorous physical activity in minutes; ODI = Oswestry Disability Index; PDI score = Pain Disability Index; PSQ-3 = pain and sleep questionnaire – 3 item; SE = sleep efficiency; TST = total sleep time; WASO = wakeup after sleep onset

Incidence and relative risk of delirium after major surgery for patients with preoperative depression: a systematic review and meta-analysis

Submission ID

63

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INTRODUCTION

Delirium is associated with a 2- to 5-fold increased likelihood of experiencing major postoperative complications.[1,2] It can lead to functional decline, higher health care expenses, long-term cognitive dysfunction, and greater mortality.[3,4] Hospitalized patients with a history of depression or clinically significant depressed symptoms have an increased risk of experiencing delirium. While the incidence of delirium after cardiac surgery for patients with preoperative depression was assessed,[5] a general estimate is lacking for adults undergoing various surgeries. We conducted a systematic review and meta-analysis to estimate the incidence and unadjusted relative risk (or relative odds) of postoperative delirium for all adults with preoperative depression undergoing a broad range of surgical procedures.

METHODS

Medline (OVID), Embase (OVID), Cochrane Controlled Register of Trials (CENTRAL), and PsycINFO databases were searched from inception to 30 June 2023. Studies included defined depression as formal pre-existing diagnosis, or the presence of clinically significant depressive symptoms assessed through patient-reported tools before surgery. Multilevel random effects meta-analyses were used to estimate the pooled incidence and relative risk of delirium. Subgroup analyses was conducted to identify important moderators of pooled estimates among various study-level covariates such as country of study, study design, inclusion of only older adults (≥ 65 yr), inclusion of only cardiac surgery procedures, inclusion of nonelective procedures, and use of formal instruments. The quality of the studies was assessed using the Risk of Bias in Non-Randomised Studies-Exposure tool. The quality of evidence for our study

objectives was assessed using the Grading of Recommendations Assessment, Development, and Evaluation criteria, modified for observational studies.

RESULTS

Forty-two studies (*n* = 4,664,051) were included in this review. The prevalence of postoperative delirium for patients with preoperative depression was 29% (95% confidence interval [CI], 17 to 43%; *I2* = 99.0%), compared with 15% (95% CI, 6 to 28%); *I2* = 99.8%) in patients without preoperative depression. The overall incidence in the combined cohorts was 21% (95% CI, 11 to 33%; *I2* = 99.8%). Patients with preoperative depression had a 1.91-fold increased risk of delirium (95% CI, 1.68 to 2.17; *I2* = 42.0%) compared with those patients without preoperative depression. Study-level covariates such as country of study, study design, inclusion of only adults, inclusion of only cardiac surgery, inclusion of only nonelective procedures, and use of validated instruments were all found to have a significant moderating effect in bivariate meta-regression models. Publication bias seemed to be present amongst the pooled studies. The certainty of evidence was “moderate” for the pooled incidence and “high” for the unadjusted relative risk between preoperative depression and postoperative delirium.

DISCUSSION

Patients with a preoperative history of depression or clinically significant depressive symptoms have a greater risk of developing post-operative delirium after surgery. Considering the frequency of preoperative depression and the significant complications associated with post-operative delirium,[4,5] greater attention in screening may allow for better informed risk assessment and discussions with patients. Future efforts should focus on developing and testing risk mitigation strategies for surgical patients with psychiatric comorbidities.

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Figure Forest plot of the multilevel random-effects meta-analysis for the incidence (1A) and relative risk (1B) of postoperative delirium for patients with preoperative depression

Figure 1A.

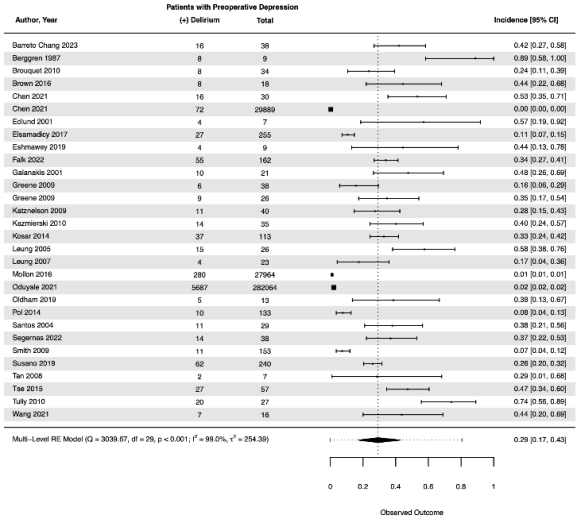
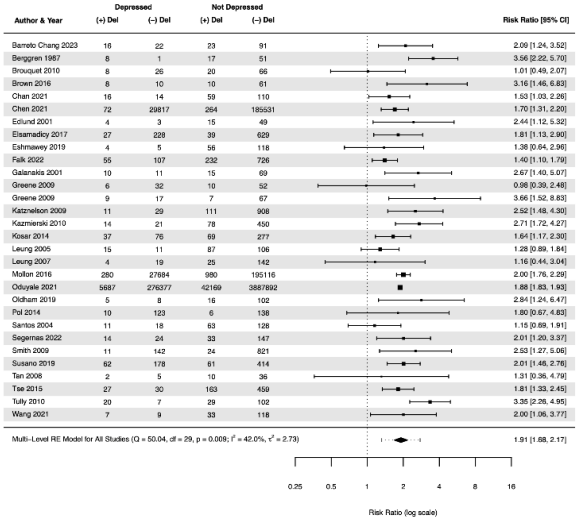


Figure 1B.



Quaternary lidocaine derivatives QX-314, QX-222, and QX-572 produce robust, long duration, concentration-dependent nociceptive blockade *in vivo*

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INTRODUCTION

The utility of currently available tertiary aminoamide local anesthetics (LAs), such as lidocaine, bupivacaine, and ropivacaine, is limited in terms of duration of action after a "single shot," undesired motor blockade, and inherent systemic and local tissue toxicity. This there is a need for a more ideal agent for clinical use. Recent preclinical research with quaternary derivatives of existing tertiary LAs heightened expectations of more "ideal" agents that produce long-lasting, nociceptive-specific blockade with low toxicity upon a single injection. Such an agent is expected to improve the quality of analgesia and pain outcomes while reducing the need for opioids in postoperative pain control. Here, we sought to investigate the relative concentration-dependent pharmacological profiles of three quaternary lidocaine derivatives, QX-314, QX-572, and QX-222, as potential long-duration alternatives to conventional tertiary aminoamide LAs.

METHODS

With institutional Animal Care Committee approval, we conducted an *in vivo* animal study with female CD-1 mice (weight, 25–35 g). We used two antinociceptive assays in the context of a sciatic nerve block model: the intraplantar hypertonic saline assay and the hot plate analgesic assay. For blockade, we performed perineural injections to animals' right sciatic nerve with a 30G hypodermic needle. In the intraplantar saline assay, hypertonic saline was injected into the middle of the ventral aspect of the footpad of the right paw. Following injection, mouse behavior was observed for five minutes, and the total amount of time the animal spent exhibiting nociceptive behavior was recorded. In the hot plate assay, animals were placed on a hot plate preheated to 50 °C. The latency to a previously defined response to the heat exposure was recorded. Each test was repeated at hourly intervals for four hours, with a sample size of 8. We used the time for responses to the nociceptive stimuli as the measure used to test for analgesic responses and the null hypotheses were that the test compounds would not produce any time-dependent analgesia whereas the scientific hypothesis was the counter one.

RESULTS

In the *in vivo* assays, all three quaternary lidocaine derivatives concentration-dependently produced robust, long-duration nociceptive blockade when compared with lidocaine. QX-572 produced the greatest efficacy, but also exhibited the most prolonged onset of action. Unlike all other drugs tested, QX-572 did not show significant effects until one hour after injection in both assays. At each time interval in the hypertonic saline assay, QX-314 produced analgesic responses of similar magnitude to those of lidocaine. Nevertheless, unlike lidocaine, its antinociceptive effects did not significantly decrease over the four-hour test period in both assays. QX-314 also produced divergent effects with regards to the two assays, showing a significant decrease in nociceptive signals between 10- and 30-mM concentrations during the hypertonic saline assay only ($P = 0.026$; $n = 8$). QX-222 was the least analgesic of all drugs tested, in both assays including when compared with lidocaine.

DISCUSSION

In the present *in vivo* animal study, the quaternary LA analogues produced effects homologous to those expected of standard tertiary LAs but with different dose and temporal relationships. The results reaffirm that quaternary agents produce long-duration sensory and nociceptive blockade. QX-572's greatly delayed onset of action compared with other tested agents is consistent with the literature. The divergent pharmacological profile of QX-314 with regards to thermal and inflammatory stimuli is consistent with the notion that a slight variation in structure can result in varying efficacies in ameliorating different modes of pain.

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The aggregate mortality risk of propofol *versus* volatile anesthesia incorporating the environmental impacts of both: a decision analysis

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20

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INTRODUCTION

Evidence suggests that the use of propofol for anesthesia maintenance is associated with an increased mortality compared with volatile anesthetic agents.[1] Volatile agents, on the other hand, are known to worsen climate change,[2] which has its own well-described adverse effects on human health including death. Which, we wondered, is more harmful overall? Our aim was to compare the aggregate mortality (direct plus indirect through environmental change) when propofol or volatile agents are used for anesthesia maintenance. We employed Decision Analysis, an analytic approach that has been used in other anesthesia scenarios:[3] the probability of the outcome of interest associated with each possible decision sequence is laid out, and the probabilities are arithmetically combined to yield the optimum strategy.

METHODS

After checking for updates, we examined a 2023 meta-analysis of randomized control trials comparing mortality from propofol and extracted the relative risk of death in surgical models compared with volatile agents. We then performed our own systematic review to find data describing the carbon footprint of isoflurane, sevoflurane and desflurane per MAC-hour of use and unit of fresh gas flow. We used published estimates of the mortality attributable to unit rise in environmental carbon dioxide.[4] We sought data on the indirect human mortality cost of propofol from waste drug pollution and the carbon cost of disposables. Finally, we combined these data into a decision analysis model with death as the outcome of interest. Since all estimates used in the model had wide ranges, we ran the model multiple times to capture both extremes in each estimate.

RESULTS

The quoted mortality risk ratio when propofol is used for maintenance compared with volatile agents is 1.25 (1.06–1.47). Our calculated annual mortality risk attributable to increases in

environmental carbon dioxide levels from volatile agent use varies from 4.26 x 10^{-6} to 1.27 x 10^{-5} lives per MAC-h, depending on which agent is considered and which extreme of the published range of carbon dioxide thus generated is used.

DISCUSSION

While the use of volatile anesthetic agents is associated with an indirect increase in human (and presumably therefore, nonhuman) mortality mediated by increases in atmospheric carbon dioxide levels, it is many orders of magnitude smaller than the additional direct mortality risk associated with the use of propofol. Climate change brings many different types of adverse consequences, but if reduction in human mortality is the outcome of interest, switching from volatile agents to propofol for anesthesia maintenance will not achieve the desired objective. Our analysis suggests that methods that avoid both modalities, such as regional anesthesia, might be better.

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