Efficiency and Quality In Post- Surgical Pain Therapy After Discharge- EQUIPPED

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Methods

This trial was conducted at a Midwestern academic medical center and community hospital using a modified 2-by-2 randomized factorial design in which participants who underwent major inpatient surgery were randomly assigned to use a participant-facing consumer health informatics phone-based app with education versus an app for data collection only. Secondarily, a clinician-facing real-time opioid prescription decision support tool embedded into electronic health records was activated halfway through enrollment. The study design followed Pragmatic Explanatory Continuum Indicator Summary guidelines to maximize broad applicability and is reported according to Consolidated Standards of Reporting Trials Extension for Factorial Randomized Trials guidelines (Supplemental Digital Content 1).

Study design and participants

Participants were eligible for enrollment if they were 19-89 years old, had access to a smartphone, and had inpatient surgery requiring at least an overnight hospitalization with anticipated discharge to home. Individuals re-hospitalized within 30 days, pregnant, unable to read the English language, discharged to a post- acute care facility, with contraindications to opioids, acetaminophen, or nonsteroidal anti-inflammatory agents, or meeting the Agency for Healthcare Research and Quality (AHRQ) definition of long-term opioid therapy (opioid use on most days > 3 months) prior to surgery were excluded. All study data were deidentified.

Randomization and masking

Participants were randomized 1:1 to the consumer health informatics smartphone-based intervention app or a control app with only data collection. Permuted block randomization (pairs) was performed using a computer-generated code within a secure central online data management system, Research Electronic Data Capture (REDCap), which was used to store and manage all participant data. No randomization was instituted for the clinician-facing intervention; instead, the decision support tool was embedded into the electronic health record to facilitate optimized opioid prescription upon discharge based on recorded inpatient use. This was implemented after half of the participants were enrolled. The principal investigator, coinvestigators, clinical coordinating center staff, participants, and statisticians remained masked to treatment assignment until the database was locked for analysis.

Sample Size Justification

To estimate power and sample size for the primary outcome, self-reported cumulative opioid use in the four weeks after discharge, investigators combined data from previous observational studies on opiates taken at one week from discharge, where variability in opioid consumption is greatest, and summed across four weeks from discharge and then log-transformed values appropriately. Investigators utilized SAS Proc Power (version 15.2, SAS Institute Inc., Cary, NC, USA) software and specified significance level alpha = 0.05 two-tailed. Across decision support tool activation status and surgical subspecialties, 300 participants per app group provided 85% power to detect minimum effect sizes (ES) of 0.23 in opioids consumed at one week and of 0.245 in opioids consumed across four weeks. Data was similarly

combined for pain intensity scores from prior studies and could detect a minimum effect size of 0.244 in pain intensity t-score at week one following discharge. Within decision support tool type and across specialty (i.e., the three-way interaction among app, decision support tool, and time), 150 participants per group provided 85% power to detect minimum effect sizes of 0.35 in opioids consumed at one week, 0.35 in opioids consumed across four weeks, and 0.35 in pain intensity t-score at one week after discharge.

Procedures

Investigators primarily tested a participant-facing app to reduce opioid intake which was designed and implemented through a user-centered design approach. The intervention app provided education on elements of pain management that could be modified by patients, including: 1) post-operative pain expectations, 2) pharmacologic alternatives to opioids, 3) opioid safety and appropriate disposal, and 4) non-pharmacological therapy, such as meditation. The control app featured the same interface but only collected patient data. The app was deployed to research team members and pilot participants for beta testing before finalization.

Baseline information was obtained from the participant in-person during the index hospitalization. During this visit, patients familiarized themselves with the format, asked questions, and received explanations regarding the apps' functionality. Following discharge, a weekly notification was sent to the participant, reminding them to complete standardized surveys and custom questionnaires during the first four weeks following discharge, a time when most opioids are consumed and when patients have shown to report consumption accurately. The day of discharge was considered day 0. If no responses were obtained via the app, participants were followed up by telephone.

In addition to the participant-facing app intervention, a clinician-facing decision support tool was operationalized for the second half of the study period for participants not requiring opioids 24 hours prior to discharge. Previous work in three diverse samples of surgical procedures found that among available predictor variables that could be incorporated into an electronic decision support tool, 24-hour pre-discharge opioid intake was most strongly associated with patient-reported post-discharge opioid intake.

Outcomes

The primary outcome was self-reported cumulative oral morphine milligram equivalents (MME) in the first four weeks after discharge. The secondary outcomes were amount of opioid prescription at discharge, supplementary opioid prescriptions within four weeks after discharge, disposal of leftover opioids within four weeks of discharge, pain intensity scores during the four weeks after discharge, and pain interference scores during the four weeks after discharge. Non-opioid prescriptions within four weeks of discharge were an exploratory outcome. Pain intensity and interference were both quantified using the National Institutes of Health Patient-Reported Outcomes Measurement Information System (PROMIS®) four-item pain intensity scale at four weeks and the four-item scale pain interference score at four weeks. All PROMIS™ scores were analyzed as standardized T- scores (mean 50, standard deviation 10).

Independent variables included sociodemographic characteristics obtained from the electronic health record and from a questionnaire provided to participants during their hospitalization: age, sex, race, ethnicity, body mass index (kg m2-1), and insurance type. Health history variables were obtained via surveys and electronic health records as necessary and included history of substance use disorder, PROMIS™ Sleep Disturbance Score, Patient Health Questionnaire-(PHQ-8) score, pre-operative opioid use, preoperative benzodiazepine use, preoperative gabapentinoid use, and preoperative antidepressant use. Clinical characteristics included the primary surgical subspecialty for the requisite hospital stay, multiple procedures performed during admission, total in-hospital opioid intake, pain score at discharge, and length of hospital stay.

Adverse events were monitored. For this study, an adverse event was considered as one requiring more than two additional opioid prescriptions within two weeks of discharge and/or access of confidential information by a non-authorized person. We considered a serious adverse event as all-cause mortality and/or re-hospitalization for any reason.

Statistical analysis

Baseline balance on potential confounding characteristics was assessed using absolute standardized difference (ASD), calculated as the difference in means or proportions divided by the pooled standard deviation. A variable was considered imbalanced if the ASD was greater than 0.16.

For the primary analysis, the effect of the intervention app on self-reported cumulative opioid use in the four weeks after discharge was modeled by log-transforming the outcome variable and then fitting a linear regression model with the app treatment group as the covariate. The treatment effects were estimated as ratio of geometric means. A sensitivity analysis was conducted using quantile regression to test the robustness of results to outliers. A model was fit with an interaction between app and decision support tool groups to evaluate potential multiplicative effects between the groups. Analysis was on a modified intention-to-treat basis, excluding participants that did not engage with the intervention or answer survey questions. There were no partial responses to the opioid-related outcomes. Missing data from pain-related survey responses were imputed from the mixed effects model.

For the secondary analysis, the effect of the intervention app on opioids prescribed at discharge was modeled by log-transforming the outcome and fitting a linear regression model with the app treatment group as the covariate. The effect of the intervention app on supplementary opioid requirements in the four weeks after discharge, opioid disposal, and non- opioid prescriptions in the four weeks after discharge was evaluated using a logistic regression model. The effect of the app on pain intensity and interference t-scores was evaluated by fitting linear mixed models with fixed covariates for app treatment group and time (categorical), and random effects for participant identification code. No interim analyses were planned because the population studied was not considered high risk for adverse events, the interventions were generally considered not harmful and to prevent alpha dilution.