Evaluating the use of sublingual sufentanil in patients with suboxone treatment who are undergoing ambulatory surgery- a case series

Introduction

Despite widespread public awareness programs and pain management recommendations, opioid use disorder (OUD) remains a significant medical challenge[1]. Opioid use disorder is a chronic replacing illness with considerable mortality and morbidity.[2] One of the long term management programs to avoid opioid use relapse is to include an opioid agonist (methadone or buprenorphine) in the management regime.[3, 4] According to the recent publication, the number of Medicaid-covered prescriptions for buprenorphine increased almost fivefold nationally — to 6.2 million from 1.3 million — between 2011 and 2018.[5]

Although studies have reported socioeconomic disparities in receiving treatment between Methodone and buprenorphine, Montefiore Medical Center has played a pivotal role in providing buprenorphine treatments to its low-income patients since the FDA approval.[6] According to the audit, there are currently well over 1000 patients in the system on Suboxone, and thousands more in the community receive Suboxone from private practice practitioners.

The treatment of acute pain, especially postoperative pain in patients taking buprenorphine, is particularly challenging.[4, 7] The high receptor binding affinity, the long half-life, and partial agonism of buprenorphine may inhibit the analgesic actions of traditional opioids, hence the potential for uncontrolled postoperative pain and serious adverse events.[7, 8]

To fulfill targeted medical needs in 2018, the FDA has approved sublingual sufentanil (DSUVIA), an opioid analgesic.[9] DSUVIA is indicated for the management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.[9] DSUVIA is restricted to use in certified medically-supervised health care settings – such as hospitals, surgical centers, and emergency departments – for administration by a health care professional.[9] Dsuvia has previously approved by the European Medicines Agency in July under the brand name Dzuveo.

In the era of an opioid crisis, especially the number of surgries performed is increasing, and patients who are on maintenance therapy for opioid disorders need more robust strategies for their postoperative pain management. Current postoperative pain management has several limitations. Intravenous morphine has a delayed half-life and a higher propensity for opioid-induced adverse events.[10] Even though hydromorphone has a quicker onset of action compared to morphine, the adverse event profiles are similar, and some studies suggesting a higher rate of sedation and CNS related adverse events.[11, 12] The lipophilic nature of fentanyl results in a quick onset of action but prompting supplemental doses for adequate pain relief. Similarly, other lipophilic opioids such as sufentanil, alfentanil, and remifentanil, can have an even more abrupt offset of analgesia due to brief initial distribution phases and/or rapid metabolism following IV bolus administration, and are therefore rarely used for postoperative analgesia.[11]

Sufentanil has a high affinity and potency at the mu-opioid receptor, making this an ideal drug of choice for patients on Suboxone. The highly lipophilic nature of sufentanil allows for prompt uptake from the sublingual tissues and cross the blood brain barrier in a relatively shorter period of time, a 6.2 minute

$t_{1/2ke0}$ compared to the 2.8 hours $t_{1/2ke0}$ of intravenous morphine.[13] Additionally, the average interdosing interval of SST in this study was 185 minutes over 12 hours, suggesting that the administration's sublingual route results in an extended duration of analgesia compared with the IV bolus administration of lipophilic opioids, such as fentanyl or sufentanil.[14] The time from peak plasma concentration (Cmax) to 50% of Cmax for sublingual sufentanil (2.5 hours) is extended 25-fold compared with bolus IV sufentanil administration of the same dose. Finally, unlike morphine and hydromorphone, sufentanil also avoids the issue of active metabolites that can lead to prolonged, untoward effects, which can complicate postoperative care and affect patient discharge.[15]

The safety and efficacy of sufentanil have been demonstrated in different types of surgeries. After hip or knee arthroplasty, patients who received sublingual sufentanil reported lesser postoperative pain compared to placebo.[14] Similar results were reported by patients who had undergone open abdominal surgery. [15]Additionally, in one of the recent publications, the use of sublingual sufentanil in the preoperative period resulted in reduced opioid usage in the post-operative period and shorter time in the postoperative anesthesia care unit.[16]

In this case, series, we are testing the hypothesis that sublingual sufentanil (Dsuvia) will improve postoperative pain management in the PACU in ambulatory surgery patients taking Suboxone.

Primary Endpoint – We will evaluate the total amount of morphine equivalence (MME) in the perioperative period (defined as combined total opioid used intra-op and in the PACU).

Secondary Endpoint(s) – We will evaluate the time to fit to discharge from the PACU, the need for additional opioids and time to take the first additional opioid within 24 hours after being discharged from the hospital, and finally, the adverse events in the intraoperative period , PACU and in the 24 hours after being discharged from the PACU (i.e., nausea, vomiting, itching, hypotension, dizziness.)

Methods

Study Design:

Prospective case series study.

Inclusion criteria

- Age range 18-100 years
- Currently taking Suboxone
- ASA physical score 1-3
- Able to provide a signed informed consent
- General anesthesia (either endotracheal intubation or laryngeal mask airway) or MAC (monitored anesthesia care)without the use of regional anesthesia

Exclusion criteria

- Known allergic reactions to Dsuvia and its excipients
- Severe respiratory illness including exacerbation of asthma attack
- Significant intraoperative hemodynamic instability
- Use of Regional anesthesia techniques

Informed Consent

According to the Montefiore standard of care, to prepare patients for surgery, the perioperative team contact patients within 1-3 days before the surgery. During this phone call, patients are given all the instructions regarding the surgical preparation, and the operative team makes sure all the needed medical records are in place. During this phone call, patients will be specifically asked about suboxone use, and an email will be sent to the research team to inform the details of the suboxone patients. The research team will screen the patients and those patients fulfilling the inclusion-exclusion criteria will be called on the day before surgery for their interest in participating in a research study. Interested patients will be provided with the study details, and all their questions will be answered. The signing of the consents will take place on the day of the surgery, an investigator associated with the study will be responsible for obtaining the informed consents.

In terms of surgery and anesthesia, the routine standard of care practiced in our hospital will be maintained for all the subjects enrolled in the study. During the study period, all the intraoperative and postoperative patient pain management guidelines will be standardized. According to the standard of practice in our institution, induction of anesthesia will take place. After induction of anesthesia, instead of intra-op and post-op Fentanyl 50mcq as needed, the patients will receive sublingual sufentanil (Dsuvia) intra-op and post-op. Detailed sublingual sufentanil is described in the next paragraph. Patients will be discharged home based on the discharge criteria followed at our institution. One of the research associates will call the patient 24 hours after discharge from the PACU to collect the information regarding their post-discharge opioid use, current pain score, adverse events, and information regarding the ED visits.

Study Objective Assessments

A research associate will be collecting the data prospectively and from the medical records. All the assessments will be coordinated with the standard of care administered at our hospital.

Study Medication and Storage

The sponsor of the study is responsible for providing the study medication. The patient or the insurance will not be billed for the study medication. Study medication will be stored in the research pharmacy at Hutch. All appropriate storage instructions will be followed, and the pharmacist will be responsible for the drug audit. On the day of surgery for an enrolled subject, research personnel will retrieve medication from the pharmacy and deliver it to the physician for administration to subjects.

Sublingual sufentanil (Dsuvia) Study Protocol Pain Medications:

Pre-op:

Acetaminophen 975mg PO

Intra-op for induction (doses as per standard):

IV Midazolam

IV Fentanyl

IV Lidocaine

IV Propofol

After induction and before incision

Ketamine .35-.5 mg/kg IV

Dsuvia 30mcg SL (1st dose)

Postop:

If pain < or = 4/10,

Give no additional medications

If pain > 4/10

give Dsuvia 30mcg SL (2nd dose)

if 30 minutes after Dsuvia 2nd dose & pain is >4/10

give Ibuprofen 800mg IV

if 60 minutes after Dsuvia 2nd dose & pain is >7/10

give hydromorphone 0.4 mg IV

Interim Analysis

We are planning to conduct an interim analysis to evaluate the use of a single dose of Dsuvia in the intraoperative period. For this purpose, if 8 of the first 15 patients require a second dose of Dsuvia in the PACU, then the protocol will be changed to give the 2nd dose of Dsuvia in the OR at 15 minutes (or more) before extubating (and more than 1 hour since the 1st dose). The rest of the protocol will stay the same.

Comparison group

The comparison group in this study will be randomly selected from a cohort of the patients satisfying inclusion and exclusion criteria. The time frame for the comparison group will be the first Dsuvia patient to the last Dsuvia patient. For the comparison group, all the data points will be collected retrospectively. For comparison, group data points after the discharge from the hospital will not be collected. We are requesting a waiver of consent and HIPAA authorization for the comparison group as this will be

conducted retrospectively. A waiver will be needed because subjects may not be possible due to reasons such as relocation, wrong contract information given, or are no longer being seen at our institution.

Statistical analysis

We are conducting this study as a pilot study. This pilot study's sample size is calculated based on the assumption that approximately 70% of the patients receive at least one dose of rescue opioid in the PACU. As this drug's efficacy in reducing the rescue opioids used in the PACU in this population is not studied previously, we plan to use a 50% rate reduction for calculating the sample size in this pilot study. According to our calculation estimate, we need to study 30 patients (alpha=0.05 and 1-Beta=0.85) in each group. The study will not be powered for secondary outcomes.

Descriptive statistics will be used to report all baseline demographic and clinical characteristics such as (age, gender, type of surgery, medications, ASA status, comorbidities). The primary endpoint amount of opioids used in the perioperative period will be compared using Wilcoxon rank-sum tests, and categorical variables such as adverse events and the number of patients requiring additional opioids will be analyzed using chi-square analysis or Fisher's exact tests. All the analysis will be two-tailed, and a p-value of <0.05 is considered statistically significant.

Data Management

All study data will be collected and entered into the computer database. Each subject will be assigned to a random number code, and the key linking the code and the subject identifier will be stored in a locked cabinet. The computer database will be password protected and will be kept on the HIPAA compliant Montefiore drive. The research manager is responsible for auditing the consistency of the data transcribed from the paper CRF to the computer. A protocol violation log will be maintained, and all protocol violations will be reported to the IRB and DSMB. The planned interim analysis (halfway through the recruitment) will be mainly focused on the additional dose of opioids in the PACU rather than the efficacy of the NMB reversal.

DSMB

The data safety monitoring board will be comprised of an anesthesiologist and a surgeon. All unanticipated serious adverse events will be reported to the DSMB. In the event of unanticipated serious adverse events, the continuation of the study will be at the discretion of DSMB and IRB. Periodic DSMB meetings will evaluate the occurrence of any study-related adverse events.

Human Safety

The FDA label for Dsuvia states that the most common adverse events associated with the drug are nausea, headache, vomiting, dizziness, and hypotension.[9] However, these occurred in less than 2% of patients studied. According to the FDA advisory committee briefing, the safety profile of Dsuvia is well established and backed with 30 years of experience.[9]

As previously referenced, the study related to the 2018 approval of Dsuvia showed that sulfinate was effective in the management of moderate to severe acute pain.[9] It is worth noting that the use of Dsuvia is to occur under strict guidelines in a medically supervised setting by a healthcare professional.[9] This allows for a reduced risk of misuse and abuse.

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