Wearable Device for Prevention of Opioid-Induced Hypoxemia

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Amendments:

Protocol date changed from September 16, 2020 – November 10, 2020 Version 21:

Page 4 updates in Primary Efficacy Outcomes

Protocol date changed from May 26, 2020 Version 18 - to September 16, 2020 Version 19:

Page 7 of 14 in the Subject Selection (Added)

We will also enroll up to 25 pre-pilot patients which will allow us to better understand and “de-bug” the system and therefore maximize effective data acquisition for the trial itself.

Page 12 of 14 at the end (Added)

There is a small degree of discomfort associated with wearing the Oxalert device, and we ask patients to bring the device back to the Clinic or mail it back to us in pre-paid envelopes. As an incentive to wear the Oxalert, we propose to pay patients $3/hour of use, up to $500 which will fully cover the pre-hospital and post-hospital days, along with up to five days of hospitalization.

Protocol changed March 18, 2021, version 24: Full statistical analysis plan.

Specific Aims

We propose a pilot randomized trial of the Oxalert EPO (Enhanced Pulse Oximeter) in surgical patients who are at high risk of opioid-induced respiratory compromise. Primarily, we will determine the feasibility of a full randomized control trial to assess the extent to which the Oxalert EPO reduces postoperative hypoxemia. The anticipated primary hypothesis for the full future trial is that Oxalert EPO alerts will reduce the time-weighted average of SpO_2 below a threshold of 90%.

Aim 1

We will evaluate the feasibility of a fully randomized validation trial for the Oxalert EPO. All patients will wear the Oxalert for 24 hours preoperatively in the monitoring only mode (no alerts), throughout hospitalization up to six days, and for 24 post-discharge hours. Randomization will be to Oxalert in monitor-only mode or to its normal mode which provides progressive audible and tactile alerts for hypoxemia. **Randomized assignment will start after surgery and continue through up to six days of hospitalization and after discharge.**

Feasibility will be defined by: 1) a single-center enrollment rate of at least two patients per week at the Cleveland Clinic Main Campus; 2) the extent to which the system is tolerated, defined as the fraction of time during the initial six post-operative in-hospital days that patients wear the device; and, 3) the frequency of hypoxemic episodes detected by the Oxalert EPO that generate an alert in the hospital.

Aim 2

We will evaluate efficacy outcomes that might be included in a future definitive trial. While under-powered in this pilot, the results will guide a realistic sample-size estimate for the future trial.

Primary efficacy outcomes

1. Time-weighted average SpO_2 below a threshold of 90% during hospitalization up to 6 days.
2. Number and duration of in-hospital postoperative desaturation events (saturation <90%) lasting at least 2 min.
3. Number and duration of hypoxemic episodes (saturation <90%) during the initial 24 post-discharge hours lasting at least 2 min.
4. Time-weighted average SpO_2 < 90% during the preoperative baseline assessment, time-weighted average SpO_2 < 90% during the post-discharge assessment, and the difference between them.

Secondary outcomes

1. Patient evaluation of device comfort/tolerability, including discomfort from the alerts.
2. Nursing evaluation of device convenience and function.

Background

There are over 70 million surgeries performed annually in USA. Postoperative pain is a ubiquitous problem among the US population. Up to 70% of surgery patients have moderate to severe pain, especially within the first 72 hours[1,2]. Opioid analgesics are the most effective analgesics, especially for management of the moderate to severe postoperative pain. On the other hand, sleep apnea is common, largely because obesity is common[3]. Both increase sensitivity to opioids and presumably increase the risk of postoperative insufficiency[5].

Some opioid-induced complications are common, but not especially serious, including nausea, vomiting, ileus, confusion, and dizziness[6]. Of importance, opioids also decrease the respiratory rate and alveolar ventilation, resulting in hypercarbia, respiratory acidosis, and hypoxemia[6]. Hypoxemia (low hemoglobin saturation) from opioid-induced respiratory depression is usually not clinically apparent, compromise wound healing, cause brain dysfunction, promote myocardial ischemia, and even progress to death[7-9]. All these outcomes are considered important measures of hospital quality and safety[10,11].

Postoperative respiratory compromise is common as well as respiratory arrests[12]. Standard post-operative monitoring is based on a “spot-check” model, in which vital signs, including oxygen saturation, are determined and recorded every 4-6 h[13,14]. From Sun et al [15], we know that 37% of postoperative patients have contiguous SpO_2 <90% lasting at least an hour. 21% of the patients experienced ≥ 10 min/h with SpO_2 <90%. Disturbingly, nurses monitor at 4-hour intervals missed 90% of all serious desaturation episodes[15]. Even if increasing the frequency of nursing assessments were practical, it would be unlikely to detect all respiratory insufficiency events.

According to Stone[16], the incidence of nocturnal hypoxemia is 50% with patient-controlled analgesia. Since patients undergoing surgical procedures are being discharged earlier and earlier[17], it is likely that many continue to experience hypoxemic episodes at home, especially during sleep.

FDA-cleared continuous saturation monitoring systems for in-hospital use are currently commercially available[18-20]. They are battery powered, untethered, and can directly be connected to electronic record systems. However, monitoring alone may not prevent ventilator complications if clinicians do not recognize desaturation quickly and intervene appropriately. An alternative is a device that both detects hypoxemia, and alerts patients to the problem. Arousal is often sufficient to awaken patients' robust voluntary control of breathing, reverse hypoxemia and respiratory arrest. Consistent with this theory, it is fairly easy to give patients sufficient opioid to decrease or stop normal ventilation, but preserve voluntary breathing in response to command. Even when audible commands fail, patients will often breathe in response to tactile stimulation.

One such device is the Apnea Prevention Device (APD)[21], which is a prototype that has a continuous monitor, alarm headphone, and tactile nerve stimulation. However, the system tethers patients and is thus impractical even in hospitals, much less at home. An alternative is the Oxalert EPO which is a small (92 X 53 X 21 mm), battery-powered, and wrist-worn apnea prevention device. The system continuously monitors SpO_2 and generates audible voice prompts when the saturation is <90% for at 2 min. The audible prompts will then continue until saturation increases to ≥90%. When saturation remains low for an additional 1 min, a mild electrical shock will provide tactile stimulation, with intensity increasing four times every 20 seconds to an intense, but safe maximum.

Compared to existing proven alternatives, the "point-of-care" Oxalert EPO provides a more tolerable, effective, promptly diagnosis of opioid-induced hypoxemia. Then the Oxalert EPO automatically evokes arousals to terminate respiratory depression and prevent arrest from relatively opioid overdose. It might make opioids safer both in hospital and home setting.

Methods

The trial will be conducted with IRB approval and a written informed consent will be obtained from adults scheduled for non-cardiac surgery with general anesthesia. All

patients will be enrolled at the Cleveland Clinic Main Campus. The trial will be registered at ClinicalTrials.gov before the first patient is enrolled.

Subject selection

We will enrich the study population to enhance the number of desaturation events by enrolling patients who are at increased risk for respiratory insufficiency. Specifically, we will focus on patients scheduled for laparoscopic or open major abdominal or pelvic surgery whose analgesia is primarily opioid-based. We will further restrict enrollment to obese patients (body mass index ≥25 kg/m^2) who are likely to have respiratory compromise. Sample size for the proposed pilot trial will be 40 valid patients. We will also enroll up to 25 pre-pilot patients which will allow us to better understand and "de-bug" the system and therefore maximize effective data acquisition for the trial itself. Both men and women will be recruited, and we will encourage under-represented minorities to participate.

Inclusion criteria

1) Adults having major laparoscopic and open abdominal or pelvic surgeries;
2) Body Mass Index ≥25 kg/m^2
3) American Society of Anesthesiologists physical status 1-3;
4) Age 18-85 years old;
5) Able to understand and consent to the trial and fully participate;
6) Anticipated primary opioid analgesia after surgery;
7) Expected duration of hospitalization at least 24 hours after surgery;
8) Consenting at least a day before anticipated surgery.

Exclusion criteria

1) Epidural analgesia (field and fascial plane blocks permitted);
2) Pre-operative SpO_2 <95%;
3) No wrist available for the study;
4) Severe hearing loss;
5) Lack of English language fluency;

6) Serious hearing deficit (unable to understand normal speech in a quite environment);
7) Serious peripheral neuropathy (unable to feel pin prick at wrist).

Protocol

At least a day before surgery, patients will be approached and consented in the pre-anesthetic consult and evaluation (PACE) clinic. Vital signs will be measured, per routine, including SpO_2. The protocol will be explained, and interested patients will be given a brief demonstration of the Oxalert, including audible prompts and the sensation produced by the electrical stimulator.

Participating patients will be given an Oxalert to take home with them. The device will be set to a record-only mode, with no alerts will be generated. Patients will be asked to wear the device for at least 24 hours. The device will thereafter be turned off in time, brought to the hospital on the day of surgery or sent back to the investigators in a pre-paid mailer. Only those who wish to continue will remain in the study.

Enrolled patients will receive routine nursing care, standard physiologic monitoring, and analgesic administration. Supplemental oxygen will be administered according to nurse discretion. Participation in the study will not alter the types or amounts of analgesics provided which will follow clinical routine. The PACU and ward nurses caring for study patients will be introduced to the protocol and the device. Vital sign and other monitoring will be exactly per clinical routine, usually at 4-hour intervals, but more often as clinically indicated.

On the day of surgery, enrolled patients will be randomized 1:1 without stratification. Randomization will be based on computer-generated codes using random-sized blocks. Investigators will receive individual assignments from a web-based system that will be interrogated in the recovery unit after surgery. Allocation will thus be concealed until the last practical moment. Randomization will be to monitor-only (no alerts) or Oxalert in normal mode which includes progressive audible and tactile stimulation in response to saturation <90% lasting more than 2 min.

An Oxalert EPO will be strapped to each patient's wrist, and standard electrocardiogram surface electrodes will be placed on the dorsum of the hand and connected to the nerve stimulator. The Oxalert devices will be programmed per randomization (monitoring and alerts versus monitoring without alerts) and data collection will be set to "on." Data collection will continue throughout hospitalization, up to 6 postoperative days. As necessary, de-identified data will be down-loaded onto a secure Cleveland Clinic computer and transferred to Redcap. The memory card of the Oxalert EPO will then be refreshed.

Patients will be monitored for an additional ≈24 hours after discharge. Monitoring after discharge will be done according to the assigned group for each patient. The study will be blinded to the extent practical. Devices with active and deactivated alerts will look identical. Patients who receive alerts will know that they have active systems, but those who have yet to receive an alert will not know if their system is deactivated or if an alert simply was not necessary.

The high saturation alarm will be disabled. Alarms for heart rate will be set to the minimum (≈30 beats/min) and maximum (≈120 beats/min) since heart rate is not an outcome of interest. For purposes of the proposed trial, the threshold will be a saturation <90% continuously maintained for 2 min. When these criteria are met, the Oxalert EPO will trigger continuous audible prompts ("Please take a breath and check the finger sensor") will begin. Tactile stimulation will begin 1 min later at a low level, and ramp up 4 times at 20-second intervals, to a safe but uncomfortable maximum intensity. The brief 290-micro-second pulses are delivered 2/second (120 Hz) through electrode pads on the dorsum of the wrist. Both audible prompts and stimuli of up to 35 milli-amperes will continue until SpO_2 rises above 90% whereupon the device will reset and audible and tactile prompts cease. Patients can discontinue alerts by pressing a button at any time.

Measurements

Demographic and morphometric characteristics will be recorded at PACE clinic, including sex, age, race, height and weight. Vital signs will be recorded, including baseline of SpO_2.

Oxalert EPO comfort and tolerability will be evaluated by phone shortly after patients complete their home monitoring. Patients will also be reminded to turn off the machine, bring or send the machine back.

Anesthetic and procedural details will be recorded electronically as usual. Intraoperative and postoperative opioid use will be calculated in equivalent amount.

Monitoring with Oxalert EPO will begin in the postanesthesia care unit and continue until the patient is discharged from the hospital (from surgery day until up to postoperative day 6). During hospital stay, the equipment status checking and data download will be completed once a day. The Oxalert EPO will be continued to be used for 24 hours after discharge according to the subject's assigned group after randomization. Therefore, the configuration of either active alerts or blinded monitoring without alerts will be performed throughout hospital stay as well as discharge.

Patients' evaluation of device comfort and tolerability will be queried at discharge day. During hospitalization, one nursing staff responsible for the enrolled subject will be given inform sheet, voluntary to participate in an anonymous questionnaire to evaluate the convenience of the device near the end of a nursing shift.

Patients will be called on the second discharged day to ask about 24-h opioid consumption and evaluate adverse events. Patients will also be reminded to send back the Oxalert EPO using a prepaid mail. De-identified data from the Oxalert EPO will be downloaded to a trial computer, and from there to a secure REDCap trial database.

Data Analysis

SpO_2 trends will be recorded and averaged in 1-minute increments for analysis. SpO_2 values <60% will be discarded as artifact (only 0.09% of all values).

The demographic and morphometric characteristics of patients in the blinded and un-blinded groups will be tabulated and absolute standardized differences will be computed. POD1-POD6 or discharge, whichever first. Summarize after removing gaps. The frequency and duration of desaturation events (SpO_2< 90%) will be compared using

two-tailed t-tests if normally distributed, or Wilcoxon tests if not, with $P<0.05$ being considered statistically significant. Patient's tolerance and nursing experience will be compared qualitatively.

Detailed Statistical Analysis Plan (outline.

The demographic and morphometric characteristics of patients will be tabulated and absolute standardized differences will be computed.

We will also report the number of patients in each group who dropped out of the trial, and the reason (s). [**technical failure** / one patient dropped out after 5 minutes. Remove this one from all analyses, but report as a technical failure.]

Primary efficacy outcomes

1. Time-weighted average SpO_2 below a threshold of 90% during hospitalization up to 6 days*, and separately for the 24-hour post-discharge period.*
-- mirror histograms of TWA < 90% ; histograms by group,

- *Mean (SD) and median (Q1, Q3), min, max, percent zero for TWA, by group;*
- *Compare groups using WRS test and median difference (CI)*
- ***Repeat all of above for AUC < 90% * minutes**.*

2. Number and duration of **in-hospital** postoperative desaturation events (saturation <90%) lasting at least 2 min. Same for initial 24 **post-discharge period.**

-- summary stats on number per patient (0, 1, 2, 3, etc); include sum per group.
-- use WRS to compare groups on number per patient; median diff (CI).

3. Difference between preoperative baseline and post-discharge 24 hour time-weighted average SpO_2 < 90%.

--- descriptive summaries on change from baseline to post d/c (post minus pre) Time-weighted average SpO_2 < 90% during the preoperative baseline assessment, time-weighted average SpO_2 < 90% during the post-discharge assessment, and the difference between them (post minus pre).

. -- Between groups: compare groups on difference between post-discharge 24 hours and preoperative TWA < 90% using Wilcoxon rank sum test and median difference (CI).
-- Within group: assess whether significant change from baseline to post-d/c 24 hrs --- Wilcoxon signed rank test. Could be paired t-test if differences look normal.

Secondary outcomes

3. Patient evaluation of device comfort/tolerability, including discomfort from the alerts.
   --- summary stats and WRS test. 5 levels.

4. Nursing evaluation of device convenience and function – WRS test.
   -- summary stats. 5 levels.

Feasibility will be defined by:

1) a single-center enrollment rate of at least two patients per week at the Cleveland Clinic Main Campus;

-Summarize enrollment: total N enrolled over what time period, and average N/week.

2) the extent to which the system is tolerated, defined as the fraction of time during the initial six post-operative **in-hospital days** that **patients wear the device**; and,

3) **Percent of time successful records were made**, defined as the percent of time in each period that usable SpO2 monitoring data was retrieved and usable– independent of whether the device was being worn or not.

Record separately for the three periods: the pre-hospital 24 hours; the initial six post-surgical hospital days; and the post-discharge 24 hours.
-- summarize time that patient should have been able to records data, time of successful recording and percent of total time there were successful recordings.
-- compare groups on percent of total time there were successful recordings using WRS test.

4) Estimate the frequency of hypoxemic episodes detected by the Oxalert EPO that generate an alert in the hospital. Since device does not record if alerts were given, we use the collected SpO2 data to summarize for each group the frequency of desaturation events lasting 1, 2, 3, 4 …. ≥10 minutes numerically and using histograms.

Human Subjects Protection

The study will be approved by the IRB at the Cleveland Clinic. Written informed consent will be obtained. Patients will be free to exit the trial at any time. They will also

be given the option to have the frequency of awakenings decreased, if poorly tolerated, by lowering the SpO_2 thresholds used to trigger those awakenings. The trial will be registered at ClinicalTrials.gov.

All routine nursing assessments and clinical treatments (including supplemental oxygen if necessary) will continue as usual. Therefore, nothing about the proposed study will in any way increase patient risk except for the Oxalert itself which is powered by a rechargable 3.7-volt battery. Patients will thus be untethered and free to move around. The device consists of essentially a commercial pulse oximeter connected to a circuit resembling a nerve stimulator of the type that is used routinely during anesthesia. Please see the Electrical Engineering Analysis provided with this application.

The Oxalert EPO is not yet cleared by the Food and Drug Administration; we therefore request a non-significant-risk (NSR) device exemption. A Data Development Plan has been submitted to and discussed with the FDA/CDRH Anesthesia Division. In support of the NSR exemption, the Anesthesia Division of the FDA has agreed to consider a De Novo or PMA submission without the results of a full clinical outcome trial being completed before pre-marketing approval because of its great potential benefit to patients. At this point they are not requiring an Investigational Device Exception (IDE). The proposed pilot trial is designed to provide information that will help the investigators, and the FDA optimally design a trial that might support FDA clearance. We provide three documents related to electrical safety, including two independent engineering analyses.

At the Cleveland Clinic Main Campus, 21% of patients have postoperative saturations below 90% for at least 10 minutes; 8% of patients have postoperative saturation below 90% for at least 20 minutes; and 8% of patients have saturations below 85% for more than 5 minutes. Post-operative desaturation is thus common and prolonged. Routine vital signs, usually at 4-hour intervals miss 90% of serious desaturation episodes.[15] The only aspect of our protocol that is non-standard is an extra saturation monitoring with Oxalert EPO, and the associated audible and tactile stimuli. Standard vital signs monitoring will continue to be used per current routine care.

Participation in the proposed trial is thus likely to benefit patients, at least in the alert group, whereas those assigned to monitoring only will be no worse off.

There is a small degree of discomfort associated with wearing the Oxalert device, and we ask patients to bring the device back to the Clinic or mail it back to us in pre-paid envelopes. As an incentive to wear the Oxalert, we propose to pay patients $3/hour of use, up to $500 which will fully cover the pre-hospital and post-hospital days, along with up to five days of hospitalization.

Change Log

Protocol version 21 dated 11/10/2020 is based on pilot patients. It is the protocol that will be used for formally randomized patients. Any subsequent changes will be detailed below.

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