Original Article

The effect of ampule size of fentanyl on perioperative intravenous opioid dosing

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Abstract

Background and Aims: There are limited data on the effect of ampule size on drug dosing. The objective of this study is to determine the effect of ampule size on perioperative opioid dosing and post-anesthesia care unit (PACU) outcomes.

Material and Methods: This was a retrospective review of patients undergoing robotically assisted laparoscopic radical prostatectomy before and after a 5-ml fentanyl ampule was discontinued. The primary outcome was intraoperative opioid administration divided into fentanyl at induction of anesthesia, total fentanyl, and total opioid. Secondary outcomes observed in PACU included the opioid administered, visual analog scale (VAS) pain scores, postoperative nausea and vomiting, and length of stay in PACU.

Results: A total of 100 patients (50 PRE and 50 POST) were included. In the intraoperative opioid administration, mean (SD) of fentanyl at induction was 117.0 (49.3) in PRE group and 85.0 (35.4) μg in POST group ($P < 0.01$). The total fentanyl requirement was 247.0 (31.0) in PRE group and 158.5 (85.1) μg in POST group ($P < 0.01$). The total opioid in intravenous morphine equivalents (IVME) was 34.1 (5.8) in PRE group and 23.2 (6.8) mg in POST group ($P < 0.01$). Among the secondary outcomes, mean (SD) of IVME of opioid was 7.7 (8.2) in PRE group and 9.9 (8.1) mg in POST group ($P = 0.18$). The VAS pain score on arrival was 0.7 (1.4) in PRE group and 3.8 (3.3) in POST group ($P < 0.01$). The cumulative VAS pain score was 2.3 (2.0) in PRE group and 3.3 (2.2) in POST group ($P < 0.01$). The length of stay was significantly more in POST group, 193.8 (75.8) minutes, as compared with PRE group, 138.6 (61.0) minutes ($P < 0.01$).

Conclusions: A change in the ampule size significantly affected intraoperative dosing, PACU pain scores, and PACU length of stay in patients undergoing robotically assisted laparoscopic radical prostatectomy under general anesthesia. This was explained by clinician's desire to conserve the drug and avoid the complex process of narcotic waste disposal.

Keywords: Ampule, anesthesia, opioids, surgery

Introduction

Opioids have been widely used for perioperative analgesia. Intravenous (IV) fentanyl is well designed for this role due to its pharmacokinetic profile which provides predictable rapid onset and short duration of action.[1,2] Numerous studies have been performed to quantify the amount, type, and even route of perioperative opioid administration based on the surgical technique, patient specific factors such as gender, and even external factors.[3-5] It is common during major surgical procedures to administer the fentanyl at induction of anesthesia and early in the procedure, followed by an opioid of longer duration of action such as morphine or hydromorphone. In post-anesthesia care units (PACU), these 3 drugs are also typically used for postoperative analgesia.

Until 2011, fentanyl was available at our institution in 2 ml (100 μg), 5 ml (250 μg), and 20 ml (1000 μg) ampules

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in the standard concentration of 50 μg/ml. For major surgical procedures, the 5 ml ampule was frequently used. In late 2011, the 5 ml ampule was discontinued by the manufacturer, and the 2 ml ampule was exclusively used for most surgeries, except for cardiac and liver transplantation. Thereafter, we perceived a reduction in the amount of fentanyl administered during major surgery and we contemplated the effect this had on total perioperative opioid dosing. A search of MEDLINE and PubMed databases did not identify any studies examining alterations in clinician opioid drug dosing after a change in the available ampule size.

Our primary hypothesis was that the absence of the 5 ml ampule resulted in a reduction in the amount of fentanyl administered at induction of anesthesia, a reduction in total fentanyl administered during surgery, and a reduction in the total dose of all IV opioids during surgery. Our secondary hypothesis was that the absence of the 5 ml fentanyl ampule resulting in reduced surgical opioids had an effect in PACU on pain levels, requirements for postoperative opioids, postoperative nausea and vomiting (PONV), and length of stay prior to inpatient unit transfer.

Material and Methods

Approval was obtained from the Mayo Clinic Institutional Review Board (protocol 13-009765), and requirement for the patient written informed consent waived. The study design was a retrospective medical record review in an academic tertiary care medical center. Inclusion criteria included American Society of Anesthesiology physical status I-IV patients undergoing robotically assisted laparoscopic radical prostatectomy (RALP) between the years 2008 to 2010 and 2012 to 2013. This population was selected as the surgery is elective, has standardized techniques with predictable duration in our institution, includes patients who consistently receive a combination of fentanyl combined with long-acting IV opioid, and results in an overnight admission. The years 2008 to 2010 and 2012 to 2013 were chosen to allow adequate number of patients before and after the 5 ml fentanyl ampule became unavailable in late 2011. Exclusion criteria included patients with opioid tolerance demonstrated by the presence of extended-release daily oral opioids on their preoperative medication list.

Patients from 2008 to 2010 (n = 50; PRE) and 2012 to 2013 (n = 50; POST) who met the criteria were selected before and after the fentanyl ampule size change. All patients were cared for in a care team approach with an anesthesiologist medically directing either a certified registered nurse anesthetist or resident physician. All resident physicians and certified registered nurse anesthetists were able to independently obtain and administer opioids. All patients underwent general endotracheal anesthesia with propofol, fentanyl, succinylcholine and/or non-depolarizing neuromuscular blocker, sevoflurane or isoflurane, and prophylactic ondansetron, and many received hydromorphone. All fentanyl were 50 μg/ml concentration with 2 and/or 5 ml ampules used in PRE group, and only 2 ml ampules in POST group. In the PACU, all patients were treated with fentanyl, hydromorphone, and morphine as single agent or combined, and rescue antiemetic as needed. Drugs in all locations were administered as IV bolus with no infusions.

Background data were collected including age, weight, ASA classification, duration of surgery from incision to completion of skin closure in minutes, and percentage of cases distributed among 5 individual surgeons. Primary outcome was intraoperative IV opioid administration divided into fentanyl dose in μg at induction of anesthesia and intubation, total fentanyl during surgery, total non-fentanyl opioids (morphine or hydromorphone), and total opioid. Data regarding the specific use of 5 ml and 2 ml ampule sizes were collected. Each anesthetic was examined for the consistency of technique and use of adjunctive analgesic and antiemetic medications.

Secondary outcomes incorporated electronic health record data obtained from PACU arrival until discharge to the inpatient unit. These included total opioid received in PACU, and total perioperative IV opioid dose defined as the sum of all opioids administered from induction of anesthesia until the PACU discharge. All opioid dosing with the exception of intraoperative fentanyl was converted to intravenous morphine equivalents (IVME) using the standard accepted conversion of morphine 10 mg = fentanyl 100 μg = hydromorphone 1.5 mg.[6] Visual analog scale pain score (0–10) was assessed on PACU arrival when the patient first responded, and subsequently every 15 minutes. A mean pain score was calculated using the sum of all recorded PACU scores. Length of PACU stay in minutes was obtained, and presence of PONV was determined using administration of at least 1 rescue antiemetic as criteria. Respiratory depression in PACU was identified by the use of naloxone for opioid reversal or any documentation of airway intervention resulting from opioid over sedation.

Sample size and power considerations

The sample size justification was based on comparisons between groups of the primary outcome: total intraoperative fentanyl between groups. Assuming Type I error is 0.05, with 45 patients per group, we had at least 80% power to detect a 0.6 SD difference in the primary outcomes.

Statistical analysis

Descriptive statistics were used to summarize the study data. To test the hypothesis on the effect of IV fentanyl ampule size on perioperative opioid usage, two-sample *t* test was used to compare the means for continuous variables. Pearson χ^2 test was used for categorical variables to determine if a significant difference existed between the 2 groups after intravenous fentanyl ampule size change. Results were considered statistically significant at $P < 0.05$. Analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Background information is summarized in Table 1, and primary and secondary outcomes are summarized in Tables 2 and 3. All patients received propofol, non-depolarizing neuromuscular blockade, sevoflurane or isoflurane, reversal with neostigmine/glycopyrrolate, and ondansetron. The presence of other analgesics and antiemetics was similar between groups. In PRE group, 15 patients received 15 or 30 mg intraoperative ketorolac, 6 patients received 4 mg intraoperative dexamethasone, and 2 patients received 300 mg preoperative oral gabapentin. In POST group, 12 patients received 15 or 30 mg intraoperative ketorolac, 5 patients received 4 mg intraoperative dexamethasone, and 2 patients received 15 mg intraoperative ketamine.

Additional data on ampule size use were analyzed with the primary outcomes. Thirty-six (72%) PRE group patients received exactly 250 μg of intraoperative fentanyl with a mean duration of surgery of 187 minutes. Of the remaining 14 (28%) patients of PRE group, 13 received a dose that was a factor of 100 (200 or 300 μg) or 350 μg, achieved using one 100 and one 250 μg ampule. Therefore, 49 (98%) PRE group patients received a dose with no waste of fentanyl at the end of surgery. Forty-six (92%) POST group patients received an intraoperative total of fentanyl that was a factor of 100 (range = 100–400 μg) when only the 2 ml vial was available, with no waste. No adverse respiratory depression events were noted in the PACU in any of the patients (no naloxone or definitive airway interventions reported).

Discussion

Studies have been conducted in anesthesia on the appropriate dose of opioids based on perceived patient requirements and associated factors such as patient age, weight, gender, and comorbid conditions.[7] Opioid doses are cited in wide ranges, based on simultaneous administration of other anesthetics and estimation of patient requirements considering many

Table 1: Patient and surgical background PRE and POST fentanyl ampule size change

	PRE (2008-2010) (*n*=50)	POST (2012-2013) (*n*=50)	*P*
Age (years), Mean (SD)	64.4 (6.4)	64.0 (11.8)	0.81
Weight (kg), Mean (SD)	88.9 (11.4)	89.0 (15.2)	0.98
ASA classification (%)	I: 6, II: 68, III: 26	I: 6, II: 64, III: 28, IV: 2	0.78
Surgical time (min) Mean (SD)	190.1 (51.0)	209.6 (57.5)	0.08
Operations performed per surgeon (%)	A: 16, B: 26, C: 14, D: 26, E: 18	A: 14, B: 34, C: 18, D: 26, E: 8	0.60

ASA=American Society of Anesthesiologists

Table 2: Primary outcomes in robotically assisted laparoscopic radical prostatectomy PRE and POST ampule size change

	PRE (2008-2010) Mean (SD) (*n*=50)	POST (2012-2013) Mean (SD) (*n*=50)	Δ Mean (SE)	*P*
Fentanyl at induction (μg)	117.0 (49.3)	85.0 (35.4)	32.0 (9.9)	<0.01
Total intraoperative fentanyl (μg)	247.0 (31.0)	158.5 (85.1)	88.5 (6.2)	<0.01
Intraoperative non-fentanyl opioid morphine equivalent (mg)	9.4 (4.5)	7.3 (5.2)	2.1 (0.9)	0.04
Total intraoperative opioid morphine equivalent (mg)	34.1 (5.8)	23.2 (6.8)	10.9 (1.2)	<0.01

Table 3: Secondary outcomes in robotically assisted laparoscopic radical prostatectomy PRE and POST ampule size change

	PRE (2008-2010) Mean (SD) (*n*=50)	POST (2012-2013) Mean (SD) (*n*=50)	Δ Mean (SE)	*P*
PACU opioid morphine equivalent (mg)	7.7 (8.2)	9.9 (8.1)	−2.2 (1.6)	0.18
Pain score on PACU arrival (VAS 0-10)	0.7 (1.4)	3.8 (3.3)	−3.1 (0.3)	<0.01
Cumulative mean PACU pain score (VAS 0-10)	2.3 (2.0)	3.3 (2.2)	−1.1 (0.4)	<0.01
PACU length of stay (min)	138.6 (61.0)	193.8 (75.8)	−55.2 (12.2)	<0.01
Presence of PONV (%)	12	26		0.13

PACU=Post-anesthesia care unit, VAS=Visual analog scale, PONV=Postoperative nausea and vomiting

factors including opioid tolerance.[8] In non-anesthesia settings, medications are typically ordered by a provider and administered by nurse. Anesthesia care provided a unique opportunity to examine the effect ampule size can have on dosage as it is determined and directly administered by the provider.

Our study showed that a reduction in fentanyl ampule size significantly decreased intraoperative dosing with 27.4% less fentanyl at induction, 36.0% less fentanyl during surgery, and 32.0% less total opioids. Interestingly, intraoperative non-fentanyl opioids also decreased 22% (9.4 mg to 7.3 mg) without a change in their ampule sizes, although cumulative reduction in total intraoperative opioid was predominantly driven by reduced fentanyl (24.7 mg to 15.9 mg in IVME). We speculated that using exclusively a 2 ml fentanyl ampule in POST group, resulting in less fentanyl administered, created conditions where providers delivered less additional opioids during surgery.

Two phenomena explain reduction in dosages after the ampule size change. First, individuals often have a desire to conserve. This is especially evident in health care where high drug costs lead to a focus on expense reduction. The cost of wasted drugs in anesthesia is well documented. In 2000, Gillerman and Browning examined 6 specific anesthetic drugs in over 25,000 patients and noted costs of unused or partially used syringes totaling $165,000.[9] One year later, Weinger reviewed 166 anesthesia cases and observed $1,802 in drugs were wasted.[10] In 2012, Chaudhary and colleagues demonstrated significant costs through wasted IV drugs, especially propofol, rocuronium, vecuronium, and neostigmine.[11] It is notable that the majority of anesthesia costs are dependent on human resources, with a smaller percentage of medication costs.[12]

A second explanation relates to the tedious process of controlled substance disposal. Strict regulation is necessary to ensure patient and employee safety, and all health care facilities should have processes for appropriate documentation of unused narcotics to discourage abuse and diversion.[13] Opioid abuse is a well-recognized risk for anesthesia providers.[14,15] Fear of inadvertent waste inaccuracy is a source of substantial stress for anesthesia providers. During 2008 to 2013, our facility used a 2-provider waste verification process, with review and potential discipline in the event of recurrent inaccuracies. In 2014, hospital pharmacists began collecting all opioid waste and compared this with the amount documented as given to patients, with random quantitative and qualitative testing of returned drug.

We suggest that the anesthesia providers may avoid the narcotic waste process by administering an entire opioid ampule when possible. This is common with fentanyl versus longer action opioids as fentanyl is frequently dosed earlier in surgery, with total dose perceived to have less effect on speed of emergence. Further evidence of this is highlighted where 98% of PRE group patients received either exactly 250 μg of fentanyl, an amount attainable using entire 250 μg and 100 μg ampules, or an amount using entire 100 μg ampules. Ninety-two percent of POST group patients received an amount that was a factor of 100 μg, when only the 2 ml vial was available. Waste of morphine or hydromorphone was greater where only 35% of patients received an amount that was divisible by the ampule size of 10 mg or 2 mg, respectively.

Patients in POST group, who received less fentanyl, had notably higher pain levels versus PRE group patients on PACU arrival, and cumulatively, this was associated with prolonged time until discharge to the inpatient unit. Length of stay in the PACU has been shown to directly correlate with pain intensity on arrival.[16] The higher pain level in POST group was detected by PACU nurses and treated with 2.2 mg IVME more opioid versus PRE group; however, this did not achieve statistical significance ($P = 0.18$). We attributed the higher pain levels observed in POST group to the use of the smaller fentanyl ampule, emphasizing the effect ampule size can have on immediate post-surgical analgesia. PONV was 14% less in PRE group (12% versus 26%); however, this did not achieve statistical significance ($P = 0.13$).

During the years 2008 to 2013, there were no major changes in the surgical or anesthetic approach to RALP. As this study was retrospective, the anesthetic could not be standardized; however, anesthesia was similar in all patients, with general endotracheal inhalational anesthesia, balanced IV opioids, without regional techniques. Trocar site tissues were infiltrated with bupivacaine by a surgeon. Liposomal bupivacaine was not available. Ketorolac and dexamethasone use was balanced in both groups, and other agents including gabapentin and ketamine were used in only 2 patients per group, and no acetaminophen. It was not until 18 months after the last patient data were assessed that the first formal enhanced recovery protocol with emphasis on multi-modal non-opioid analgesia appeared in our practice, and that was in colorectal surgery. PACU medication order sets and care were unchanged during the data collection time-frame, and there were no specific drug cost saving efforts. We feel strongly that enhanced recovery perioperative care philosophy did not impact our findings as the anesthetics and time-frame simply do not support that. The reduction in fentanyl use was immediately apparent with the absence of the 5 ml ampule, prompting the development of this study.

This study had limitations. First, we limited our scope to RALP patients as their care and clinical course was quite

predictable during the study years. Future efforts could examine if this effect is present with other standardized surgical populations. In addition, we did not follow patients beyond the recovery room to assess more downstream effects. We did not assess the behavior of nurse anesthetists, residents, or attending physician anesthesiologists independently, as all cases were performed in a care team model with shared decision making. The large number of physicians and anesthetists involved in these surgeries precluded examination of specific individual provider behavior. Hospital bed availability could have impacted PACU length of stay; however, bed availability fluctuates, and considering patients were selected over a period of years, this was likely balanced between groups. There were no specific efficiency efforts to affect PACU length of stay during the years studied. We understand that this retrospective study lacked the ability to control certain external factors. It would be exceptionally difficult to execute a similar study prospectively in a modern hospital environment with strict formulary and an internal review process which places emphasis on patient and provider safety. Clinicians would also rapidly notice an artificial change in the size of an ampule they were provided, and this could affect the quality of data in a prospective study.

Conclusions

We are confident that our study identifies the powerful effect fentanyl ampule size can have on dosing during surgery and highlights a potential effect on PACU pain levels and PACU length of stay. We suspect that ampule size may influence the dose of other commonly used drugs in anesthesia, and recognition of this phenomenon is of great importance to the manufacturers, pharmacists, and clinicians especially during formulary changes or times of drug shortages.

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Conflicts of interest
There are no conflicts of interest.

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