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Improving postoperative pain control after cesarean delivery with enhanced recovery in patients on buprenorphine therapy

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Abstract

Introduction

Prescription drug abuse presents a significant challenge to the management of postoperative pain. Pain control amongst the opioid addicted patient can be especially challenging. We aimed to improve pain control after cesarean delivery with enhanced recovery in patients who are on buprenorphine medication-assisted therapy for the treatment of opioid addiction.

Materials and Methods

We conducted a pilot study by implementing a protocol using liposomal bupivacaine injected at the time of cesarean delivery. Patients were then given 500mg oral acetaminophen every 4 hours, 800mg oral ibuprofen every 8 hours and 0.3mg IV buprenorphine every 6 hours as needed. Patients' maintenance dosing of buprenorphine was divided into doses throughout the day. In addition, patients were ambulated 4 hours after surgery and had their catheters removed from their bladder as soon as they could safely ambulate. Eleven patients were prospectively recruited and then compared to a retrospective sample of seventeen patients.

Results

Patients in the treatment group reported 27% lower pain scores ($p < 0.05$) with 55% and 100% achieving a mean pain score 3 and 4 or less, respectively ($p < 0.05$). Patients who were in the treatment group utilized 51% less breakthrough IV buprenorphine with 45% declining IV buprenorphine, however these did not reach statistical significance. Hospital charges were reduced by \$1,589 ($p < 0.01$).

Discussion

Our enhanced recovery protocol is an effective alternative to traditional pain control and is associated with a significant reduction in both pain scores and use of breakthrough IV buprenorphine as well as lower charges.

Keywords

buprenorphine, ERAS, pain control, cesarean delivery, liposomal bupivacaine

Introduction

Prescription drug abuse creates a significant problem in the United States. With 41.5 overdoses per 100,000, West Virginia has among the highest overdose rates in the country.¹ Buprenorphine is an approved form of medication-assisted therapy and is recommended for the treatment of addiction in pregnancy.² Pain control for this patient population can be especially challenging, as literature regarding this subject is lacking. Further complicating pain management in this population is the high opioid maintenance dose utilized by this population. Using standard opioid conversion ratio of 1mg sublingual buprenorphine to 10mg oral morphine,^{3,4} a patient taking 16mg daily of sublingual buprenorphine is already taking 160mg opioid daily. For comparison, this is the same as taking 21 oxycodone 5mg tablets, 8mg of IV hydromorphone, 53mg of IV morphine or 533mcg of IV fentanyl daily.^{3,4} Cesarean delivery accounts for 31% of

all deliveries, making it one of the most common operations on reproductive age women.⁵ This therefore necessitates evaluation of post-cesarean pain protocols.

Certain protocols have been developed specifically to help patients recover more rapidly after surgery. Enhanced Recovery after Surgery (ERAS) protocols utilize multimodal pain control and local anesthesia combined with early feeding, ambulation and catheter removal to expedite patient recovery.⁶⁻¹² Several studies have shown that ERAS protocols improve patient pain control and increase patient satisfaction while decreasing opioid use.⁶⁻¹² Liposomal bupivacaine is a formulation of the local anesthetic bupivacaine that has been encapsulated by lipids in order to increase the effective duration of the drug by several days.¹³ One study found that using liposomal bupivacaine along with ERAS protocols decreased length of stay following a cesarean delivery without any increase in adverse events.⁶

There is a paucity of data evaluating any manner of pain control after cesarean delivery in patients who struggle with opioid addiction, let alone those on buprenorphine medication-assisted therapy. Data evaluating liposomal bupivacaine is limited to the aforementioned study. We hypothesize that implementation of an ERAS protocol that utilizes liposomal bupivacaine at the time of surgery will improve pain control and decrease the use of IV buprenorphine for breakthrough pain in patients undergoing a cesarean delivery who are in opioid-addiction recovery programs that utilize buprenorphine for medication-assisted therapy.

Materials and Methods

We conducted an ambispective pilot study to evaluate postoperative pain management strategies. This started with a retrospective analysis of the current standard of care. At our institution, patients who undergo scheduled cesarean delivery receive spinal anesthesia consisting of 13mg bupivacaine, 10mcg of fentanyl and 0.2mg morphine. Currently, in addition to the On-Q® and continuing current home maintenance buprenorphine dose as scheduled, patients receive IV ketorolac 30mg every 6 hours followed by 10mg oral ketorolac every 6 hours, as well as 0.3mg IV buprenorphine every 6 hours as needed. The On-Q® system utilizes percutaneous catheters that infiltrate the abdominal and pelvic cavities with buprenorphine over a 2 to 3 day period. After surgery, patients are allowed regular diet 1 hour after surgery. The catheter is removed after 12 to 24 hours and patient is allowed to ambulate 12 hours after surgery. The retrospective analysis included patients within given time period that met inclusion criteria.

Next, we prospectively implemented an ERAS protocol previously described in gynecologic oncology literature.¹³ This protocol consisted of the spinal anesthesia, as mentioned above, followed by 266mg (20mL) diluted into an additional 20 mL of normal saline of liposomal bupivacaine injected subcutaneously along the length of the incision at time of skin closure. Postoperative pain was controlled with 500mg of oral acetaminophen scheduled every 4 hours, 800mg of oral ibuprofen every 8 hours and 0.3mg IV buprenorphine every 6 hours as needed for breakthrough pain. Maintenance buprenorphine dose was then divided into 4 times daily dosing. For example, if a patient takes 16mg daily of buprenorphine then they would receive 4mg every 6 hours postoperatively. Patients resumed regular diet 1 hour after surgery. In addition, patients were ambulated after 4 hours and the catheter was removed when the patient could safely ambulate.

We compared the retrospective data, which reflected the standard of care, to the data we collected prospectively following the implementation of the ERAS protocol. For the retrospective analysis, we included all eligible patients over a 1-year span. To be eligible for inclusion in the retrospective group, patients had to be at an age of 18 years or greater, at a gestational age of 34 weeks or greater, and have a non-emergent cesarean delivery at Cabell Huntington Hospital while being treated for opioid addiction with medication-assisted therapy using buprenorphine. For eligibility for inclusion in the prospective group, patients had to meet the same criteria as described for the retrospective group. With informed consent, we recruited a prospective group for the implementation of the ERAS protocol over a 6-month period. Patients were excluded from the study if any one of the above-mentioned criteria were not met.

We then conducted a retrospective evaluation of medical records for several data points. These included: patient demographics, medical comorbidities, gravidity, parity, postoperative pain scores, postoperative complications, length of stay (LOS), postoperative care charges, and IV buprenorphine use during hospitalization. Routine patient care also included the collection of urine drug screens. The administration of all postoperative drugs began when the patient left the operative suite, as recorded by the nursing staff.

Mean pain scores served as the primary outcome. On the day of surgery and postoperative days 1, 2 and 3, the mother-baby nurse recorded pain scores on a Likert scale of 0-10 with 0 representing no pain and 10 representing severe pain. The goal at our institution was for the patient to meet a pain score of 3 or less. Because other institutions use the measure of a pain score of 4 or less, both data points were recorded. We also measured several secondary outcomes, including the amount of IV buprenorphine used, LOS, nausea and/or vomiting that required the use of anti-emetics as well as hospital and pharmacy charges. These charges included the cost of the local anesthetic used intraoperatively as well as the charges for medications used to control pain and nausea and/or vomiting post operatively. A unique identifier was given to every patient. The master code for these identifiers was securely stored on a password-protected computer. The retrospective pre-implementation data and the prospective post-implementation data was compared using the Fisher Exact test and the Mann Whitney U test. Because data collection was recorded as part of routine postpartum documentation, blinding of patients, providers, and staff was virtually impossible. However, care was taken to ensure that the research staff did not interact with the patient following informed consent, except as medically necessary for routine obstetric and gynecological care. Our study protocol was approved by the Institutional Review Board who found it to be exempt from full review due to the low risk that implementing the protocol posed to the research subjects. Informed consent was also waived for those subjects in the retrospective cohort. The authors of this study do not have any financial disclosures.

Results

Seventeen patients met inclusion criteria and were included in the MARC cohort retrospective control group. Eleven patients met inclusion criteria for the prospective ERAS group for analysis. Due to the low-risk nature of the study, none of the eligible patients declined participation in the study. As shown in Table 1, overall mean age was 30.5 years with a range of 23-41 years and a standard deviation of 4.5 years. Mean BMI was 30.9kg/m² with a range of 20-42kg/m² and a standard deviation of 6.3kg/m². The ERAS group had a higher obesity rate (34.0% versus 28.4%, $p < 0.01$), however the distribution among the various classes of obesity

were similar. There were more smokers in the ERAS group 82 versus 71 percent ($p < 0.05$). All patients in both the retrospective and prospective groups were on 8mg of sublingual buprenorphine twice daily preoperatively. Pregnancy demographics, surgical characteristics and the comorbidities of hypertension and diabetes mellitus were similar between the groups. All urine drug screens were only appropriately positive for buprenorphine.

Table 1. Demographic and Surgical Characteristics (n=28)

Characteristic	Control (n=17)	ERAS (n=11)	p Value
Demographic			
Age(y)	17 [30.9 (29.0-32.9)]	11 [28.4 (26.6-32.8)]	0.50 [‡]
BMI	17 [28.4 (26.1-30.8)]	11 [34.0 (30.3-37.7)]	0.01 [‡]
Normal or overweight	12 (71)	3 (27)	0.07 [§]
Class I and II obesity	4 (24)	5 (45)	
Morbid Obesity	1 (5)	3 (27)	
Smoking			0.02 [§]
Never	5 (29)	0 (0)	
Former	0 (0)	2 (18)	
Current	12 (71)	9 (82)	
Comorbidities			
Hypertension	3 (18)	4 (36)	0.54 [§]
GHTN, Preeclampsia	2 (12)	3 (27)	
CHTN	1 (6)	1 (9)	
Diabetes Mellitus	0 (0)	1 (10)	>0.99 [§]
Pre-pregnancy	0 (0)	0 (0)	
Gestational	0 (0)	1 (13)	
Pregnancy Demographics			
Parity			>0.99 [§]
Primiparous	1 (6)	1 (9)	
Multiparous	16 (94)	10 (91)	
EGA at time of delivery	17 [38 ^{2/7} (37 ^{5/7} -39 ^{0/7})]	11 [37 ^{3/7} (35 ^{2/7} -39 ^{4/7})]	>0.99 [‡]
Surgical Characteristics			
Primary Cesarean Delivery	3 (18)	2 (18)	0.68 [§]
Indication			>0.99 [§]
Repeat	14 (82)	9 (82)	
Malpresentation	1 (6)	1 (9)	
Obstructed Labor	2 (12)	1 (9)	
Anesthesia			>0.99 [§]
Spinal	14 (82)	9 (82)	
Epidural	3 (18)	2 (18)	
Tubal Ligation	6 (40)	6 (50)	0.44 [§]
Birth Weight (g)	17 [3116 (2858-3373)]	11 [2868 (2362-3373)]	0.31 [‡]
EBL (mL)	17 [641 (588-695)]	11 [555 (483-626)]	0.06 [‡]
1 minute APGAR 7 or greater	17 (100)	10 (91)	0.39 [§]

Data are n [mean (95% CI)] or n (%)

[‡] Mann-Whitney U Test

[§] Fisher Exact

GHTN = Gestational hypertension

CHTN = Chronic hypertension or chronic hypertension with superimposed preeclampsia

Overall pain scores were 27% lower in the ERAS group (2.95 versus 4.04, $p < 0.05$), as shown in Table 2. 100 percent of patients in the ERAS group met the pain score goal of 4 or less versus 53% in the control group ($p < 0.05$). Likewise, 55% of the ERAS patients versus 18% of the control group ($p < 0.05$) met the pain score goal of 3 or less (odds Ratio 5.6, 95% CI 1.00-31.3).

The odds ratio for the pain goal of 4 or less could not be calculated as 100 percent of the ERAS group met this goal.

Table 2. Primary Outcomes (n=28)

Characteristic	Control (n=17)	ERAS (n=11)	Change	p Value
Markers of Effective Pain Control				
Pain Score				
Day 0	17 [4.37 (2.82-5.93)]	11 [3.82 (1.66-5.98)]	- 13%	0.66 [‡]
Day 1	17 [4.77 (3.54-6.00)]	11 [2.77 (1.47-4.07)]	- 42%	0.03 [‡]
Day 2	17 [4.02 (3.02-5.02)]	11 [3.46 (2.43-4.50)]	- 14%	0.46 [‡]
Day 3	16 [3.03 (1.94-4.12)]	8 [1.81 (0.00-3.63)]	- 40%	0.23 [‡]
Mean	17 [4.04 (3.31-4.76)]	11 [2.95 (2.26-3.63)]	- 27%	0.04 [‡]
Achieved Pain Goal (≤ 3)	3 (18)	6 (55)		0.05 [§]
Achieved Pain Goal (≤ 4)	9 (53)	11(100)		0.007 [§]
Markers of Ineffective Pain Control				
Days with Mean Score > 5				
1 or more days	8 (47)	7 (64)		0.29 [§]
2 or more days	6 (35)	1 (9)		
3 or more days	1 (6)	0 (0)		
Days with Mean Score > 7				
1 or more days	2 (12)	0 (0)		0.70 [§]
2 or more days	1 (6)	0 (0)		
Persistent pain with mean pain score of:				
5 or greater	3 (18)	0 (0)		0.21 [§]
7 or greater	1 (6)	0 (0)		0.61 [§]

Data are n [mean (95% CI)] or n (%)

[‡] Mann-Whitney U Test

[§] Fisher Exact

Similarly, ERAS patients had a lower incidence of days with significant pain, 5 or higher, at 47 versus 64 percent ($p=0.29$) and lower incidence of days with a severe pain score, 7 or higher, at 0 versus 12 percent ($p=0.70$), although these did not reach statistical significance. Likewise, ERAS subjects had a lower proportion of those who reported persistent pain of 5 or greater (0 versus 18 percent, $p=0.21$) and persistent severe pain of 7 or greater (0 versus 6 percent, $p=0.61$), however these did not reach statistical significance.

As shown in Table 3, overall IV buprenorphine use was 51% lower in the ERAS group when compared to the control group, however, this did not reach statistical significance (0.53mg versus 1.08mg, $p=0.18$). Although not statistically significant, patients were more likely to go without IV buprenorphine entirely (45 versus 24 percent, $p=0.22$). The range of opioid use in the control group was 0mg to 4.2mg with a standard deviation of 1.3mg. The range of opioid use in the ERAS group was 0mg to 1.8mg with a standard deviation of 0.7mg. While not statistically significant, patients were less likely to need a breakthrough antiemetic at 9 versus 29 percent ($p=0.21$). Day 2 discharge rate was higher in the ERAS group at 36 versus 6 percent, but likewise did not reach statistical significance ($p=0.15$). Pharmacy charges were \$603 lower (\$1581 versus \$2184, $p<0.01$). Overall hospital charges were \$1589 lower (\$10106 versus \$11695, $p<0.01$).

Table 3. Secondary Outcomes Patients (n=28)

Characteristic	Control (n=17)	ERAS (n=11)	Change	p Value
Breakthrough Narcotic Use (mg IV Buprenorphine)				
Day 0	17 [0.23 (0.09-0.37)]	11[0.25 (0.04-0.44)]	+ 7%	0.89 [‡]
Day 1	17 [0.34 (0.13-0.54)]	11[0.14 (0.00-0.28)]	- 59%	0.16 [‡]
Day 2	17 [0.35 (0.12-0.59)]	11[0.05 (0.00-0.18)]	- 85%	0.07 [‡]
Total by Day 2	17 [0.92 (0.45-1.40)]	11[0.44 (0.10-0.78)]	- 53%	0.16 [‡]
Day 3	16 [0.16 (0.02-0.29)]	7 [0.02 (0.04-0.09)]	- 83%	0.15 [‡]
Total	17 [1.08 (0.47-1.68)]	11[0.53 (0.14-0.93)]	- 51%	0.18 [‡]
Declined IV Buprenorphine	4 (24)	5 (45)		0.22 [§]
Day 2 Discharge	1 (6)	4 (36)		0.15 [§]
Needed Breakthrough Antiemetic	5 (29)	1 (9)		0.21 [§]
Postpartum Charges (\$)				
Pharmacy Charges	17 [2184 (1922-2447)]	11[1581 (1345-1817)]	- \$603	0.003 [‡]
R&B Charges	17 [9510 (9137-9883)]	11[8524 (7394-9655)]	- \$986	0.04 [‡]
Total Charges	17 [11695 (11276-12114)]	11[10106 (8883-11328)]	- \$1589	0.004 [‡]

Data are n [mean (95% CI)] or n (%)

[‡] Mann-Whitney U Test

[§] Fisher Exact

R&B = Room and board charges for both mother and infant in the postpartum period

None of the patients abandoned the protocol to return to traditional pain control methods. None of the patients in either the retrospective or prospective groups took narcotics aside from buprenorphine. With regard to the liposomal bupivacaine, none of the patients reported allergy, wound infection, injection site reaction or any other complications. Despite early ambulation and early catheter removal, we did not have any adverse events such as urinary retention or falls. All patients completed the study as no patients withdrew consent.

Discussion

Treating opioid addicted patients represents a special challenge. The goal is to avoid excess narcotics to prevent relapse while still adequately treating postsurgical pain so as to help prevent patients from self-medicating. Our protocol was associated with a 27% reduction in mean pain scores. Patients in the ERAS group were 5.6 times more likely to reach the pain goal of 3 or less with 100% of the patients reaching a mean pain score of 4 or less despite all of the control patients using the On-Q® bupivacaine system. We observed a lower incidence of persistent severe pain in the ERAS, however this did not reach statistical significance.

Our protocol appeared to be associated with dramatic reductions in IV buprenorphine use at 51%, however this did not reach statistical significance. This statistic was underpowered for this outcome due to the large variability. A secondary Mann-Whitney test showed to have 80% power with an alpha of 0.05 to detect an opioid reduction of 51% was 130 patients per group due to the variability in IV buprenorphine use, which was not feasible for this pilot study. Given the price difference between the On-Q® system and liposomal bupivacaine, and lower utilization of

expensive intravenous acetaminophen and intravenous buprenorphine, this protocol was associated with a marked reduction in pharmacy charges as well as overall hospital charges.

This study examines a unique population in that 29-73% of the subjects are obese, 26-36% of patients are tobacco users, and the subjects come from an area highly addicted to opioids. This is the first study to address pain management in patients who struggle with addiction and who are on maintenance therapy. This study is among the first that evaluates the safety and efficacy of liposomal bupivacaine after cesarean delivery. The higher proportion of patients who use tobacco in the ERAS group may have increased the IV buprenorphine use in the ERAS group, as tobacco use is associated with higher levels of narcotic use.¹⁵ However, its relationship to buprenorphine utilization is unclear and likely did not significantly alter our results. While the intrinsic validity characteristics demonstrate the lack of randomization, a preponderance of the patient-specific characteristics that increase surgical difficulty were similar among the groups.

Our study design is a unique ambispective design containing both a retrospective, before intervention, and a prospective, after intervention, component. Although blinding was impossible due to the nature of the ERAS protocol intervention, a significant amount of attention was given to avoiding bias in the data collection process. The language used to obtain informed consent was carefully chosen to avoid artificial lowering of pain scores due to patient bias. To protect against bias from the research staff, we took care to avoid interacting with the research subjects beyond providing their necessary and routine care. To ensure accuracy of pain measurements, the nurses were instructed to record pain scores the same way for all patients. In order to avoid artificially lowering pain scores, all patients had similar quantities of opioids offered to them. Due to the heavily Caucasian population that our facility serves, we were unable to draw any meaningful conclusion regarding the effect of the ERAS protocol on minorities.

Our study is a pilot study, with a relatively small sample (n=28); a larger and sufficiently powered study would require a multi-year and multi-center approach. Patients who underwent surgery earlier in the day would logically have a longer postoperative day 0 and thus use more opioids. However, this discrepancy would have a limited impact as an additional few hours of postoperative time would not account for the significant difference seen between the groups. Our study was not designed, nor intended to compare the efficacy of On-Q® and liposomal bupivacaine, rather it was designed to compare a pain management protocol that utilizes liposomal bupivacaine to a pain management protocol that utilizes On-Q®.

Liposomal bupivacaine with an abdominal binder, scheduled oral acetaminophen and ibuprofen along with intravenous buprenorphine as needed for breakthrough pain are a safe alternative to traditional methods for patients who are undergoing treatment for opioid addiction with buprenorphine after non-emergent cesarean delivery after 34 weeks. Our protocol appears to be associated with a 27 percent reduction in pain scores and 51 percent reduction in IV buprenorphine use. This study shows the promise of liposomal bupivacaine and enhanced recovery protocols in reducing pain and opioid use postoperatively. Further prospective and larger clinical trials are warranted.

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