MARKED VARIABILITY IN PERI-PARTUM ANESTHETIC MANAGEMENT OF PATIENTS ON BUPRENORPHINE MAINTENANCE THERAPY (BMT): CAN THERE BE AN UNDERLYING ACUTE OPIOID INDUCED HYPERALGESIA PRECIPITATED BY NEURAXIAL OPIOIDS IN BMT PATIENTS?

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Abstract

Objectives: To compare adequacy of peri-partum pain management with or without neuraxial opioids in patients on buprenorphine maintenance therapy (BMT).

Methods: After institutional review board approval for the study protocol, retrospective peri-partum anesthesia/analgesia data of BMT patients for five-year period were accessed and analyzed.

Results: Out of reviewed 51 patient charts, nineteen patients were found eligible for final comparative analysis. The daily amounts of peri-partum rescue analgesics with vs without neuraxial opioids were equianalgesic doses of parenteral hydromorphone (10.7 ± 13.8 mg vs 2.6 ± 0.7 mg, P = 0.45 for vaginal delivery; 16.4 ± 21.1 mg vs 5.3 ± 3.6 mg, P = 0.42 for elective cesarean section (CS)), oral ibuprofen (1.1 ± 0.5g vs 0.8 ± 0.4g, P = 0.37 for vaginal delivery; 1.1 ± 0.2g vs 1.6 ± 0.6g, P = 0.29 for elective CS), and acetaminophen (0.2 ± 0.4g vs 0 ± 0g, P = 0.56 for vaginal delivery; 0.3 ± 0.3g vs 0.2 ± 0.2g, P = 0.81 for elective CS). In the patients who underwent emergent CS after failed labor (all had received epidural opioids), there was clinical trend for higher daily amounts of peri-partum rescue analgesics (parenteral hydromorphone 35.6 ± 37.5 mg,; oral ibuprofen 1.2 ± 0.4g; oral acetaminophen 1.2 ± 0.5g), when compared with vaginal delivery patients or elective CS patients who all had received neuraxial opioids.

Conclusions: As the study was underpowered (n = 19), future adequately powered studies are required to conclude for-or-against the use of neuraxial opioids in BMT patients; and pro-nociceptive activation by neuraxial opioids may be worth investigating to improve our understanding of peri-partum pain management of BMT patients.

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Introduction

The treatment of choice for maintenance therapy in opioid-dependent pregnant patients is methadone[1]. Buprenorphine maintenance therapy (BMT) is FDA-approved for community-based treatment of opioid dependence[2], but not during pregnancy. However, women may choose to continue BMT during pregnancy if they are stable in treatment[3] or if methadone is not available or refused. In addition, the preliminary results indicate that buprenorphine-exposed fetuses and neonates have superior well-being and outcomes as compared to methadone-exposed fetuses and neonates[4-6]. Buprenorphine has high affinity for mu receptors, but only activates them partially. Moreover, based on clinical experiences and incompletely understood mechanisms/phenomena, there is an ongoing debate whether peripartum neuraxial opioids improve or worsen peri-partum analgesia in BMT patients[7-8]. Therefore peri-partum pain management becomes challenging and unpredictable in patients on BMT[9].

The goal of this retrospective analysis was to compare adequacy of peri-partum pain management with and without neuraxial opioids in patients on BMT.

Methods

After the institutional review board approval for the study protocol, the retrospective data for a five-year period (2007-2011) were accessed at an academic university's women's hospital. The pharmacy and information technology team were asked to screen the patients admitted to the obstetric floors in the abovementioned five-year period for the administration of buprenorphine in any form (sublingual, oral, intravenous or intramuscular). This pharmacy data review and analysis provided the research team with the detailed number of patients who were on buprenorphine during their hospital stay in our obstetric floors. Additionally, for accessing the patients that might have been missed by abovementioned analysis, Medical Center Business Objects as well as Medical Records were screened for inpatient admissions with the admitting diagnosis codes as 648.3 [drug dependence in pregnancy]. Subsequently, the electronic medical records (and as needed the paper medical records) of all the eligible patients were accessed for the following observation parameters:

Pre-procedure (labor epidural or cesarean section):

- Patient's age, height and weight, and ASA class
- Daily dose and route of administration of buprenorphine
- Whether patient had taken the scheduled dose before the procedure
- Any other documented pain medication

Intra-procedure:

- Type of procedure
- Whether neuraxial access was obtained
- What type of neuraxial access was obtained
- Whether neuraxial opioids were given
- Types and total doses of neuraxial opioids/local anesthetics given were calculated based on our standard practices for neuraxial medications administration and total duration of neuraxial analgesia-anesthesia
- Any other pain medication given during the procedure

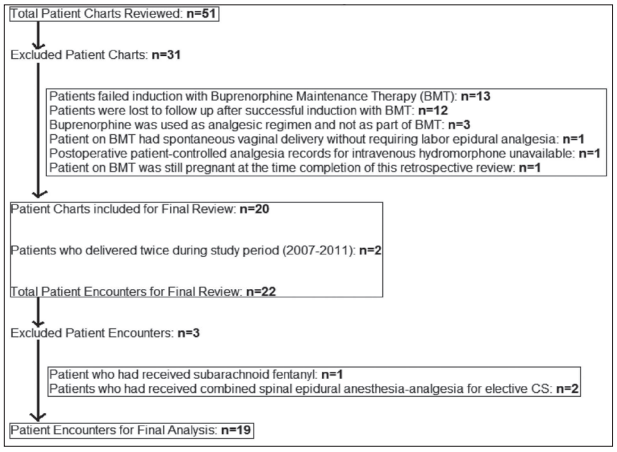
Post-procedure (till the time of discharge):

- Daily dose and route of administration of buprenorphine
- Whether neuraxial opioids were given in post-operative epidural analgesic solutions
- Type and total dose of neuraxial opioids/local anesthetics given
- Type and daily dose of non-steroidal anti-inflammatory drugs (NSAIDs) given
- Type and daily dose of parenteral opioids given
- Type and daily dose of pain medications at discharge

Subsequently, the following primary peri-partum anesthesia/analgesia data were compared between the patients who had or had not received neuraxial opioids [the patients were stratified whether they received epidural or intrathecal opioids, and whether they delivered vaginally or with cesarean section (CS)]: daily home dose of buprenorphine, daily

Fig. 1

CONSORT Diagram



equianalgesic parenteral dose of hydromorphone, total equianalgesic dose of epidural fentanyl, and daily oral doses of ibuprofen and acetaminophen received. The equianalgesic doses for the parenteral opioids were primarily calculated from the online web-applications[10-11]. Daily home dose of sublingual buprenorphine 0.4 mg was considered equianalgesic to intramuscular/intravenous buprenorphine 0.3 mg and intrathecal morphine 250 mcg was considered equianalgesic to epidural fentanyl 83 mcg[12-14]. In view of variable but not yet confirmed equianalgesia reports[15-17], intravenous ketorolac 120 mg was considered equianalgesic to oral ibuprofen 2400 mg.

For statistical analysis, ANOVA Single factor was applied to compare the means and variance of the continuous data. Chi-Square test was utilized to compare all (expected frequencies equal to or greater than 5) but extremely small sample size based proportions; a two-tailed Fisher exact probability test was used if the sample size was very small. A p-value of <0.05 was considered statistically significant.

Results

A total of 51 patient charts were reviewed; however only nineteen patient encounters remained for comparative analysis after various exclusions as shown in Fig. 1: CONSORT Diagram. Subsequently, the patients were stratified whether they had only received labor epidural analgesia and delivered vaginally (Table 1), and whether they underwent elective CS and received subarachnoid block only (Table 2). Finally, as all emergent CS patients (n = 3) had received epidural opioids, these patients were compared within the strata of patients who all had received neuraxial opioids but had differed in their mode of fetal delivery (Table 3). The daily amounts of peri-partum rescue analgesics (an indicator of adequacy of peri-partum pain relief) with vs without neuraxial opioids were equianalgesic doses of parenteral hydromorphone, oral ibuprofen, and acetaminophen as shown in Tables 1-2 and Fig. 2. Moreover, in the patients who underwent emergent CS after failed labor, there was clinical trend for higher daily amounts of peri-partum rescue analgesics when compared with vaginal delivery patients or elective CS patients who all had received neuraxial opioids (Table 3, Fig. 3). Even though our results were statistically

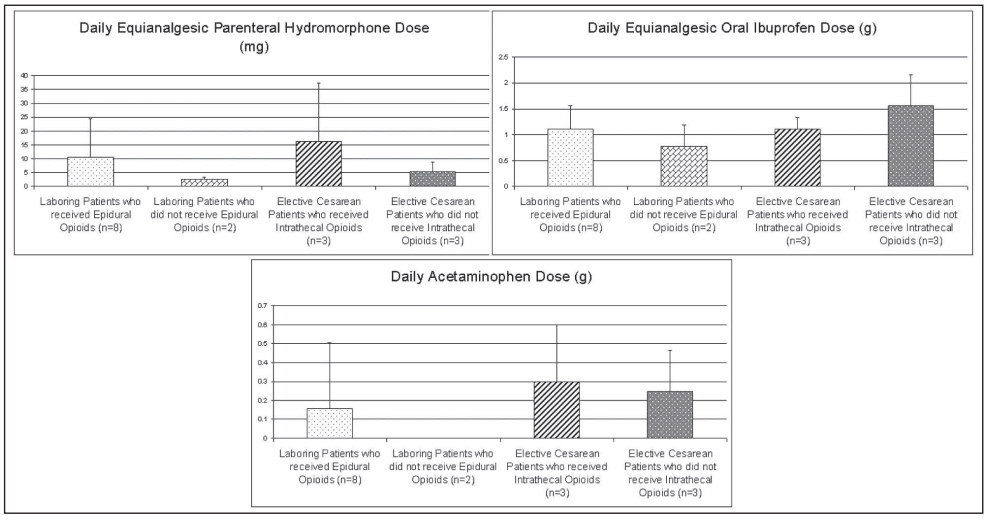


Fig. 2

Daily Peri-Partum Analgesics Requirements by Patients on Buprenorphine Maintenance Therapy in Peri-Anesthesia Period: A Comparison of Vaginally Delivered Patients and Elective Cesarean Section Patients

Table 1

Comparison Parameters (in terms of rescue analgesics) to adjudge adequacy of Peri-Partum Pain Relief with or without Epidural Opioids in Laboring Patients on Buprenorphine Maintenance Therapy

	Those who had Epidural Opioids (n = 8)	Those who did not have Epidural Opioids (n = 2)	P value
Pre-Anesthesia Parameters			
Age (yrs)	25.13 ± 5.84	24.5 ± 6.36	0.9
Height (inches)	64.63 ± 3.54	62.5 ± 3.54	0.47
Weight (pounds)	167.38 ± 21.53	139 ± 0	0.11
Pre-Anesthesia Daily Home Dose of Buprenorphine (mg)	16 ± 5.66	10 ± 8.49	0.25
Peri-Anesthesia Parameters after the institution of Labor Epidural Analgesia			
Days till Hospital Discharge (n)	3.13 ± 0.64	4 ± 1.41	0.19
Total Epidural Fentanyl Dose (mg)	0.40 ± 0.14	-	-
Total Epidural Bupivacaine Dose (mg)	164.06 ± 71.48	Unknown	-
Total Equianalgesic Parenteral Hydromorphone Dose (mg)	31.85 ± 41.58	11.05 ± 6.44	0.52
Daily Equianalgesic Parenteral Hydromorphone Dose (mg)	10.67 ± 13.82	2.64 ± 0.67	0.45
Total Equianalgesic Oral Ibuprofen Dose (g)	3.5 ± 1.82	2.8 ± 0.57	0.62
Daily Equianalgesic Oral Ibuprofen Dose (g)	1.11 ± 0.45	0.77 ± 0.42	0.37
Total Acetaminophen Dose (g)	0.5 ± 1.07	0 ± 0	0.54
Daily Acetaminophen Dose (g)	0.16 ± 0.35	0 ± 0	0.56

Table 2

Comparison Parameters (in terms of rescue analgesics) to adjudge adequacy of Peri-Partum Pain Relief with or without Intrathecal Opioids in Elective Cesarean Section Patients on Buprenorphine Maintenance Therapy

	Those who had Intrathecal Opioids (n = 3)	Those who did not have Intrathecal Opioids (n = 3)	P value
Pre-Anesthesia Parameters			
Age (yrs)	30 ± 4.58	34.67 ± 6.66	0.37
Height (inches)	62.67 ± 2.31	65.33 ± 1.15	0.15
Weight (pounds)	177.67 ± 33.26	190.33 ± 31.02	0.65
Pre-Anesthesia Daily Home Dose of Buprenorphine (mg)	13.33 ± 4.62	13.33 ± 9.24	>0.99
Peri-Anesthesia Parameters after the institution of Subarachnoid Anesthesia			
Days till Hospital Discharge (n)	3.67 ± 0.58	3.33 ± 0.58	0.52
Total Intrathecal Morphine Dose (mcg)	250 ± 50	-	-
Total Intrathecal Bupivacaine Dose (mg)	12 ± 0	12 ± 0	>0.99
Total Equianalgesic Parenteral Hydromorphone Dose (mg)	52 ± 60.81	19.07 ± 16.25	0.42
Daily Equianalgesic Parenteral Hydromorphone Dose (mg)	16.39 ± 21.08	5.31 ± 3.62	0.42
Total Equianalgesic Oral Ibuprofen Dose (g)	4.13 ± 1.36	5.33 ± 2.61	0.52
Daily Equianalgesic Oral Ibuprofen Dose (g)	1.11 ± 0.22	1.56 ± 0.60	0.29
Total Acetaminophen Dose (g)	1.2 ± 1.2	0.88 ± 0.82	0.72
Daily Acetaminophen Dose (g)	0.3 ± 0.3	0.25 ± 0.22	0.81

Fig. 3

Daily Peri-Partum Analgesics Requirements by Patients on Buprenorphine Maintenance Therapy in Peri-Anesthesia Period: A Comparison of Emergent Cesarean Section Patients within the Strata of Patients who all received Neuraxial Opioids

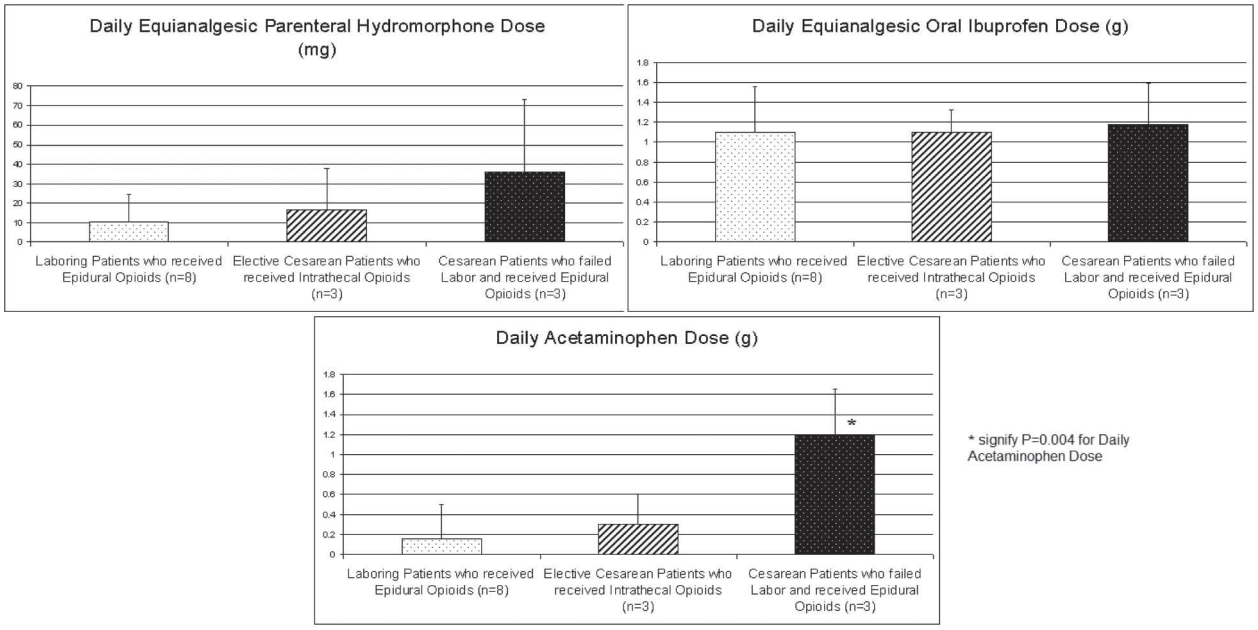


Fig. 4

Schematic Diagram of Mechanism of Action underlying the difficult Peri-Anesthesia Management with Neuraxial Opioids in Patients on Buprenorphine Maintenance Therapy (inspired from Jones)[28]. Fentanyl attaches to mu-receptor and highly stimulates it; however, buprenorphine can easily displace fentanyl from mu-receptor. Now this receptor is poorly stimulated by buprenorphine; however, fentanyl displacing buprenorphine from mu-receptor is questionable due to very strong affinity of buprenorphine to mu-receptor

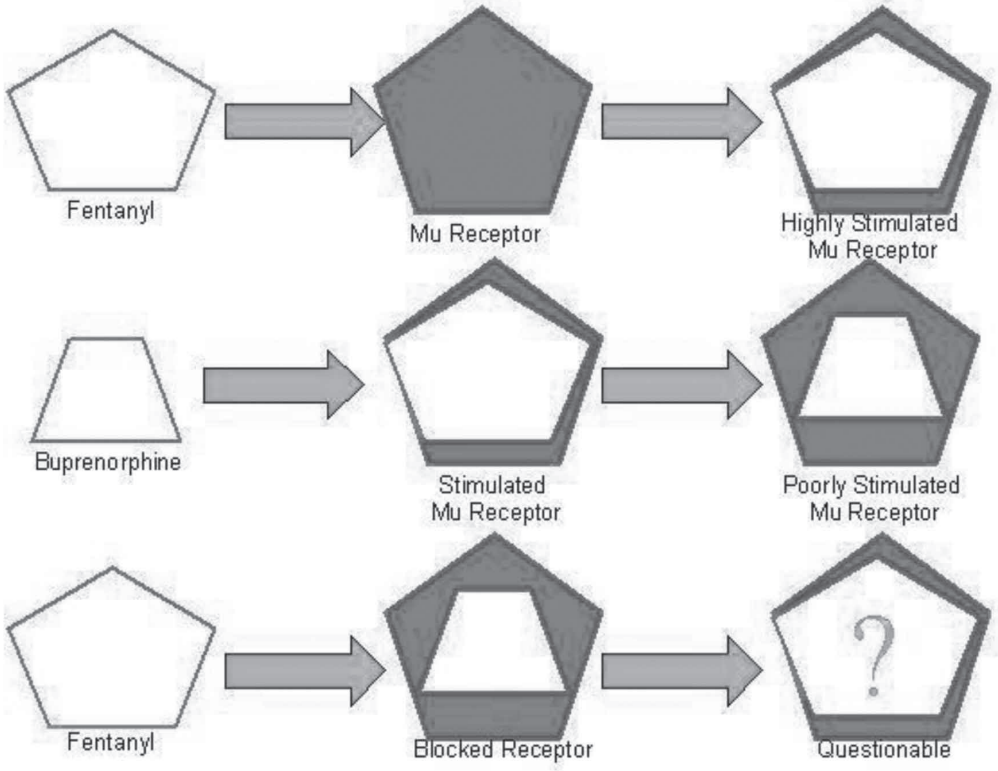


Table 3
Peri-Partum Pain Relief Parameters with Neuraxial Opioids in Patients on Buprenorphine Maintenance Therapy when compared among them based on Mode of Fetal Delivery

	Patients had Normal Vaginal Delivery (n = 8) (*From Table 1)*	Patients had Elective Cesarean Section (n = 3) (*From Table 2)*	Patients had Cesarean Section after Failed Labor (n = 3)	P Value
Pre-Anesthesia Parameters				
Age (yrs)	25.13 ± 5.84	30 ± 4.58	28 ± 2.65	0.38
Height (inches)	64.63 ± 3.54	62.67 ± 2.31	63 ± 3.61	0.62
Weight (pounds)	167.38 ± 21.53	177.67 ± 33.26	209.67 ± 13.2	0.06
Pre-Anesthesia Daily Home Dose of Buprenorphine (mg)	16 ± 5.66	13.33 ± 4.62	15.33 ± 9.02	0.82
Peri-Anesthesia Parameters after the institution of Neuraxial Block				
Days till Hospital Discharge (n)	3.13 ± 0.64	3.67 ± 0.58	4.33 ± 1.53	0.16
Type of Neuraxial Block	Labor Epidural Analgesia	Subarachnoid Anesthesia	Labor Epidural Analgesia converted to Epidural Anesthesia	-
Total Neuraxial Opioid Dose	0.40 ± 0.14 (Fentanyl mg)	0.25 ± 0.05 (Morphine mg)	0.78 ± 0.57 (Fentanyl mg)	-
Total Neuraxial Bupivacaine Dose (mg)	164.06 ± 71.48	12 ± 0	204.17 ± 95.47	-
Total Equianalgesic Parenteral Hydromorphone Dose (mg)	31.85 ± 41.58	52 ± 60.81	191.87 ± 242.84	0.15
Daily Equianalgesic Parenteral Hydromorphone Dose (mg)	10.67 ± 13.82	16.39 ± 21.08	35.62 ± 37.49	0.27
Total Equianalgesic Oral Ibuprofen Dose (g)	3.5 ± 1.82	4.13 ± 1.36	5.13 ± 2.20	0.44
Daily Equianalgesic Oral Ibuprofen Dose (g)	1.11 ± 0.45	1.11 ± 0.22	1.18 ± 0.41	0.96
Total Acetaminophen Dose (g)	0.5 ± 1.07	1.2 ± 1.2	5.11 ± 2.3	0.002
Daily Acetaminophen Dose (g)	0.16 ± 0.35	0.3 ± 0.3	1.21 ± 0.45	0.004

significant only for acetaminophen use among neuraxial opioids patients depending on mode of fetal delivery (Table 3), the clinical trends suggest that the study is underpowered and the differences in other analgesic requirements may not have reached level of statistical significance ($P < 0.05$) because very few pregnant women (nineteen in the five-year study analysis period) chose to continue BMT during pregnancy.

Discussion

Peripartum pain management encompasses analgesic coverage for the following: (a) first stage labor pain is visceral in origin and mediated through thoracolumbar spinal segments (T10-L1) secondary to inflammatory mediators released from dilated and effaced cervix, (b) second stage labor pain is somatic in origin and mediated through sacral spinal segments (S2-S4) secondary to a distended perineum, and (c) post-cesarean pain, mediated through thoraco-lumbo-sacral spinal segments (T4-S5), is a combination of somatic origin pain due to surgical incision and visceral origin pain due to uterine exteriorization.

Buprenorphine is 17-(cyclopropylmethyl)-alpha-(1,1-dimethylethyl)-4,5-epoxy- 18,19-dihydro-3-hydroxy-6-methoxy-alpha-methyl-6,14-ethenomorphinan-7-methanol. As buprenorphine is a partial agonist to the mu receptor, it stimulates the mu receptor, but at lower intensity than other opioids (partial agonism). However, as buprenorphine binds more strongly to the receptor, it can displace other opioids from the receptors. Conversely, dissociation of buprenorphine from the receptor is slow, and other

opiates may not be able to stimulate the occupied mu receptor (Fig. 4). Therefore, peripartum analgesia is unpredictable if other opioids are given concomitantly and peripartum pain management becomes challenging in pregnant patients who are on BMT for opioid dependence.

During the peripartum period of BMT patients, the dilemma for obstetric anesthesiologist is whether neuraxial opioids are required at all for efficacious peripartum analgesia. The reasons are multiple. Firstly, buprenorphine has very strong affinity to opioid receptors and hence fentanyl (the most commonly used neuraxial opioid in obstetric analgesia-anesthesia) may not be able to displace buprenorphine from these blocked receptors (Fig. 4). Secondly, fentanyl has high lipophilicity and hence cranial spread of this medication is very limited, making neuraxial fentanyl ineffective in countering supraspinal analgesic needs of BMT patients. Thirdly, there is no data in BMT patients for the use of neuraxial hydromorphone which is less potent ($1/10^{th}$) than fentanyl, but has more cranial spread due to its hydrophilicity, and is rarely used in obstetric analgesia-anesthesia[18] because of delayed onset of analgesic action as well as respiratory depression. Fourthly, supraspinal analgesic requirements may be variable and receptors in BMT patients may be insensitive to regular doses of parenteral opioid supplementation because of long half life of buprenorphine and its strong affinity to opioid receptors (spinal and supraspinal). Fifthly, the superfluous concentrations of neuraxial fentanyl molecules that are not able to displace buprenorphine molecules from anti-nociceptive receptors may then be acting on unoccupied pro-nociceptive receptors via excitatory neuropeptides and spinal dynorphin and/or descending pathway facilitation, similar to the proposed mechanisms/theories that are used to explain opioid induced hyperalgesia[19]. Finally, the superfluous concentrations of some buprenorphine molecules that are actually displaced by neuraxial fentanyl from the low affinity sites[20-21] in the spinal cord are free to act upon the orphanin FQ/nociceptin/ opioid receptor-like 1 receptor system with full agonism that consequently in itself attenuates the generalized (supraspinal and spinal) anti-nociceptive efficacy of buprenorphine[22-23]. The percentage (3-37%) of buprenorphine molecules displaced by fentanyl is dependent on the concentrations of the pre-existent buprenorphine (0.5-2 nmol/liter) in the body[24]. Consequently, the number of these displaced molecules of buprenorphine may be very small when the patient is on high to very high buprenorphine dose (8-32 mg/day). Therefore, this opioid receptor-like receptor agonism, that is unique to buprenorphine compared to fentanyl, may be minimal.

Although lacking statistical significance, our results suggest that it may be better to avoid neuraxial opioids for peripartum analgesia in BMT patients because a larger dose of peripartum rescue analgesics were required when they had received concomitant neuraxial opioids in peripartum period; in contrast to a former study[8], our retrospective analysis of nineteen patients shows the clinical trend for more rescue analgesics in both vaginal delivery as well as elective CS patients when they had received neuraxial opioids (Tables 1-2). Therefore, in our opinion, a suggested peripartum management for BMT patients would be: (a) to continue maintenance doses of buprenorphine, (b) effective epidural or intrathecal catheter placement for peripartum pain, (c) utilization of higher than usual concentrations of local anesthetic solutions to accommodate the absence of neuraxial opioids and to prevent overt sensitization of ascending pain pathways, (d) liberal use of non-steroidal inflammatory agents in postoperative periods for inflammatory cervical, perineal and incisional pain, (e) aggressive management with transversus abdominis plane block supplementation for post-cesarean incisional pain, and (f) "Last resort" supplementation with parenteral opioids with different receptor selectivity, or alpha-2 agonists and N-methyl-D-aspartate antagonists for non-resolving pain[25].

Pre-emptive sensory blockade with higher doses of epidural bupivacaine may prevent the sensitization of the pro-nociceptive pain pathways in the opioid dependent peripartum patients who are highly susceptible to opioid-induced hyperalgesia that may be precipitated in peri-operative setting or is worsened with the use of peri-operative opioids (intrathecal opioids as well as parenteral opioids). This explanation for higher requirements of parenteral opioids and poor pain control with neuraxial opioids in BMT patients has ample support in medical literature as acute opioid induced hyperalgesia[26-27]. Though

these earlier reports theorized pro-nociceptive role of intrathecal opioids even in opioid-naïve patients, the mechanism holds true (and may be to a greater degree) for opioid dependent patients receiving neuraxial opioids. Similar to higher analgesic potency and efficacy of neuraxial opioids as compared to parenteral opioids, it is logical to assume and theorize that hyperalgesic potency and efficacy of neuraxial opioids will be higher than parenteral opioids; this may particularly hold true when the anti-nociceptive receptors have been strongly occupied by pre-existent buprenorphine in BMT patients.

This study has limitations. The number of patients was very low (n = 19) and hence the study was underpowered. It was a retrospective analysis. Biochemical and molecular evidence cannot be offered for neuraxial opioid-related hyperalgesia theory in BMT patients with this small retrospective analysis. Larger randomized prospective trials are required but are needed to be done as multi-center multi-national trials due to paucity of pregnant BMT patients.

Conclusions

As the study was underpowered (n =19), future adequately powered studies are required to conclude for-or-against the use of neuraxial opioids in BMT patients; and pro-nociceptive activation by neuraxial opioids may be worth investigating to improve our understanding of peri-partum pain management of BMT patients.

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References

1. Rayburn WF, Bogenschutz MP: Pharmacotherapy for pregnant women with addictions. *Am J Obstet Gynecol*; 2004, 191:1885-97.
2. Walsh SL, Eissenberg T: The clinical pharmacology of buprenorphine: extrapolating from the laboratory to the clinic. *Drug Alcohol Depend*; 2003, 70:S13-27.
3. Minozzi S, Amato L, Davoli M: Maintenance treatments for opiate dependent adolescent. *Cochrane Database Syst Rev*; 2009: CD007210, 2009.
4. Jones HE, Johnson RE, Jasinski DR, O'grady KE, Chisholm CA, Choo RE, Crocetti M, Dudas R, Harrow C, Huestis MA, Jansson LM, Lantz M, Lester BM, Milio L: Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome. *Drug Alcohol Depend*; 2005, 79:1-10.
5. Jansson LM, Dipietro JA, Velez M, Elko A, Williams E, Milio L, O'grady K, Jones HE: Fetal neurobehavioral effects of exposure to methadone or buprenorphine. *Neurotoxicol Teratol*; 2011, 33:240-3.
6. Jones HE, Finnegan LP, Kaltenbach K: Methadone and buprenorphine for the management of opioid dependence in pregnancy. *Drugs*; 2012, 72:747-57.
7. Paranya G, Plante D, Kristensen E, Meyer M: Buprenorphine impairs intrapartum patient controlled epidural analgesia (PCEA) efficacy. Abstracts of the Scientific Papers Presented at the 39th Annual Meeting of the Society for Obstetric Anesthesia and Perinatology, May 16-19, 2007. *Anesthesiology*; 2007, 106:B1.
8. Meyer M, Paranya G, Keefer Norris A, Howard D: Intrapartum and postpartum analgesia for women maintained on buprenorphine during pregnancy. *Eur J Pain*; 2010, 14:939-43.
9. Jones HE, O'grady K, Dahne J, Johnson R, Lemoine L, Milio L, Ordean A, Selby P: Management of acute postpartum pain in patients maintained on methadone or buprenorphine during pregnancy. *Am J Drug Alcohol Abuse*; 2009, 35:151-6.
10. ANONYMOUS. MEDCALC.COM [INTERNET]: Unknown: MedCalc; c1999-2012 [updated 2010 January 27; cited 2012a March 12]. Available from: http://www.medcalc.com/narcotics.html
11. ANONYMOUS. GLOBALRPH.COM [INTERNET]: Detroit: GlobalRPH Inc.; c1993-2012 [updated 2012 March 12; cited 2012b March 12]. Available from: http://www.globalrph.com/narcotic.cgi
12. Bullingham RE, Mcquay HJ, Dwyer D, Allen MC, Moore RA: Sublingual buprenorphine used postoperatively: clinical observations and preliminary pharmacokinetic analysis. *Br J Clin Pharmacol*; 1981, 12:117-22.
13. Du Pen SL, Du Pen AR: The dilemma of opioid conversion in intrathecal therapy. *Seminars in Pain Medicine*; 2003, 1:260-4.
14. Mcpherson MA: Demystifying opioid conversion calculations: a guide for effective dosing. 1st ed. Bethesda, Maryland: American Society of Health-System Pharmacists, Inc, 2009.
15. Turturro MA, Paris PM, Seaberg DC: Intramuscular ketorolac versus oral ibuprofen in acute musculoskeletal pain. *Ann Emerg Med*; 1995, 26:117-20.
16. Neighbor ML, Puntillo KA: Intramuscular ketorolac vs oral ibuprofen in emergency department patients with acute pain. *Acad Emerg Med*; 1998, 5:118-22.
17. ANONYMOUS. CLINICALTRIALS.GOV [INTERNET]: Bethesda: U.S. National Library of Medicine; c1993-2008 [updated 2012 May 08; cited 2012c September 11]. Available from: http://clinicaltrials.gov/ct2/show/NCT01595282
18. Mhyre JM: Strategies to induce labor analgesia with epidural hydromorphone. *Int J Obstet Anesth*; 2008, 17:81-2.
19. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L: A comprehensive review of opioid-induced hyperalgesia. *Pain Physician*; 2011, 14:145-61.
20. Villiger JW, Taylor KM: Buprenorphine: high-affinity binding to dorsal spinal cord. *J Neurochem*; 1982, 38:1771-3.
21. Pergolizzi J, Aloisi AM, Dahan A, Filitz J, Langford R, Likar R, Mercadante S, Morlion B, Raffa RB, Sabatowski R, Sacerdote P, Torres LM, Weinbroum AA: Current Knowledge of Buprenorphine and Its Unique Pharmacological Profile. *Pain Pract*; 2010, 10:428-50.
22. Lutfy K, Eitan S, Bryant CD, Yang YC, Saliminejad N, Walwyn W, Kieffer BL, Takeshima H, Carroll FI, Maidment NT, Evans CJ: Buprenorphine-induced antinociception is mediated by mu-opioid receptors and compromised by concomitant activation of opioid receptor-like receptors. *J Neurosci*; 2003, 23:10331-7.
23. Khroyan TV, Polgar WE, Jiang F, Zaveri NT, Toll L: Nociceptin/orphanin FQ receptor activation attenuates antinociception induced by mixed nociceptin/orphanin FQ/mu-opioid receptor agonists. *J Pharmacol Exp Ther*; 2009, 331:946-53.
24. Boas RA, Villiger JW: Clinical actions of fentanyl and buprenorphine. The significance of receptor binding. *Br J Anaesth*; 1985, 57:192-6.
25. Koppert W, Schmelz M: The impact of opioid-induced hyperalgesia for postoperative pain. *Best Pract Res Clin Anaesthesiol*; 2007, 21:65-83.
26. Cooper DW, Lindsay SL, Ryall DM, Kokri MS, Eldabe SS, Lear GA: Does intrathecal fentanyl produce acute cross-tolerance to i.v. morphine? *Br J Anaesth*; 1997, 78:311-3.
27. Angst MS, Clark JD: Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology*; 2006, 104:570-87.
28. Jones HE: Practical considerations for the clinical use of buprenorphine. *Sci Pract Perspect*; 2004, 2:4-20.