Ibuprofen and Acetaminophen versus Ibuprofen and Acetaminophen plus Hydrocodone for Analgesia after Cesarean Section: A Randomized Controlled, Comparative Effectiveness, Equivalence Trial

The IVY trial

NCT03372382

Version Date: 05/02/2018

Ibuprofen and Acetaminophen versus Ibuprofen and Acetaminophen plus Hydrocodone for Analgesia after Cesarean Section: A Randomized Controlled, Comparative Effectiveness, Equivalence Trial

The IVY trial

Jenifer Dinis, MD

Eleazar Soto, MD

Claudia Pedroza, PhD

Baha Sibai, MD

Division of Maternal Fetal Medicine.

Department of Obstetrics, Gynecology, and Reproductive Sciences.

University of Texas McGovern Medical School.

IRB NUMBER: HSC-MS-17-0777
IRB APPROVAL DATE: 05/02/2018

Background

Opioid use after cesarean section

Currently there is an opioid abuse epidemic in the United States [1]. Contrary to common belief, One of the most common sources of drugs for abuse are prescribed medications [2]. According to the CDC, in 2015 there were 3,988,733 births, 32% of which were cesarean sections [3] thus, prescription of opioids for postpartum women may be one of the most common sources of leftover medications that have potential for abuse.

The American College of Obstetricians and Gynecologist has issued guidelines for perinatal care [4] with a section on postpartum analgesia acknowledging that opioids can be necessary after a cesarean section, especially in the first 24 hours, but there is no standard recommendation regarding the type and amount of opioid to be prescribed.

Although many studies have determined approximate opioid requirements in the first 24-48 hrs after cesarean section [5], until recently there was a paucity of data regarding patterns of use once women are discharged from the hospital. Empirically, 30 to 40 tablets of any opioid agent are prescribed upon discharge [6], Non Steroidal Anti-inflamatory Drugs (NSAIDS) are also prescribed as they can decrease concomitant opioid use and improve analgesia[7,8]. A Cochrane review published in 2015 sought to determine the effectiveness, safety and cost-effectiveness of oral analgesia for post-caesarean pain relief. This review included 8 trials that were not performed in the US, with a total of 962 women but no conclusions could be made regarding the safest and most effective form of oral analgesia due to poor quality of data [9]

The limited evidence that exists regarding postpartum patterns of opioid use indicates that practitioners tend to prescribe more drugs than what the patients may need [10]. Bartels et al [11] conducted a prospective cohort study including 30 patients undergoing cesarean section and 30 patients undergoing thoracic surgery. They sent an online survey to these patients during their postoperative period inquiring about the amount of medication consumed and storage and disposal methods for it. They found that 53% of patients had leftover opioids at 30 days postpartum.

Osmundson et al [10] analyzed data from 179 women that were prescribed opioids after c-section. The study group filled a survey regarding medication use during hospitalization and again 14 days after discharge; those still using opioids at the time of the second survey were contacted weekly until they reported discontinuation of opioid medication. The authors reported that women took opioids for a median of 8 days after discharge from the hospital and consumed a median of 75 morphine milligram equivalents, which equals 22 tablets of oxycodone 5mg or 15 tabs of hydrocodone 5mg. 75% of women had leftover pills after their postpartum period.

More recently, Bateman et[12] al enrolled 720 patients on a prospective study, patients that had undergone a c-section were contacted by phone 2 weeks after discharge to obtain information regarding use of opioid prescription. Their patients used a median of

20 opioid tablets and 83.5% of patients had leftover tablets. They reported that patient satisfaction did not correlate with amount of opioids prescribed and that the more opioids are prescribed, the more the patients use after leaving the hospital.

To date, those are the only study that has published data regarding the amount of opioids used after discharge from the hospital. Our research team is currently conducting a prospective study regarding patterns of opioid use postpartum as well as patient satisfaction, which could validate the findings mentioned above (POP study, HSC-MS-17-0293)

Mechanism of Action of Opioids

Papaver somniferum and *P. album* are the source of opium, which contains 10% morphine. Opioids bind to μ (mu), δ (delta) and κ (kappa) receptors located in the brain and spinal cord, responsible for transmission of pain signals. [13]. All opioids are metabolized by the cytochrome P450 2D6 (CYP2D6) enzymes into more active metabolites and then glucuronized in the liver for excretion. The only exception to this is Hydromorphone, which is metabolized in the liver to an inactive metabolite: hydromorphone-3-glucoronide. [13,14]

CYP2D6 exhibits great polymorphism. There are three types of patients according to this enzyme's activity [14]:

-Poor metabolizer (PM): patients with non functioning alleles for CYP2D6.

-Intermediate metabolizer (IM): function is partial due to inheritances of only one functioning allele.

-Extensive metabolizer (EM): considered normal functional status of the enzyme, resulting of inheritance of two functioning alleles for the enzyme gene.

-Ultrarapid Metabolizer (UM): inheritance of extra functioning alleles, conferring increased enzyme action.

PM and IM patients clear opioids via other compensatory CYCP450 enzymes. UM have increased accumulation of active metabolites, which can lead to opioid toxicity [15]. People with North African or middle eastern ascendance have increased likelihood of being UM [15].

Mechanism of Action of Ibuprofen

Ibuprofen reversibly inhibits COX-1 and COX-2 and the production of thromboxane, prostaglandin, and prostacyclin. Arachidonic acid diversion to the leukotriene pathway when the cyclooxygenase-catalyzed prostaglandin pathway is blocked, might result in increase in leukotriene and bronchoconstriction. This form of allergy is more common among aspirin users than ibuprofen user [16].

Inhibition of prostaglandin synthesis results in anti-inflammatory and antipyretic effects. In neonates, ibuprofen can cause closure of a patent ductus arteriosus. [16]

Mechanism of action of acetaminophen

It is known that acetaminophen has both peripheral and central anti-inflammatory properties, including COX inhibition, however the exact mechanism of analgesia has not been elucidated. It also has antipyretic effects [17,18].

Rationale for this study

Opioid use has quadrupled over the past decade with 259 million prescriptions in 2012 alone in the United States, which consumes more prescription opioid pain relievers than any other nation [1,19]. This has led to concern that there is an opioid epidemic in the United States. Undoubtedly adequate analgesia is required after a cesarean section, but it is still unclear which the most appropriate analgesic treatment is after the patient has left the hospital after a cesarean section.

According to the CDC, in 2015 there were 3,988,733 births, 32% of which were cesarean sections [3] thus, prescription of opioids for postpartum women may be one of the most common sources of leftover medications that have potential for abuse. Every 3 minutes, a woman seeks care in an emergency department related to prescription opioid misuse[19]. The rising prevalence of opioid use in pregnancy has led to a concomitant dramatic fivefold increase in neonatal abstinence syndrome over the past decade. Neonatal abstinence syndrome is a drug withdrawal syndrome that opioid-exposed neonates experience shortly after birth.

In addition, the use of narcotics while breastfeeding may lead to adverse drug reaction on the breastfeed infant. Opioid analgesia during postpartum may affect infant alertness and suckling vigor. More importantly, the use of codeine or tramadol in breastfeeding women may result in fatal overdoses in extreme cases depending on the child drug metabolism. Due to those concerns, the US FDA issued a warning and contraindications for the use of codeine and tramadol in breastfeeding women in 2017. The statement suggests using opioids other than codeine or tramadol such as morphine or hydromorphone; which may not have the same effect of the neonate or infant but certainly can have serious effect on the mother in cases of overdose or misuse [19].

The use of narcotics for pain control as outpatient therapy after a cesarean delivery appears to be standard practice in the United States. However, in many countries the use of narcotics is limited after cesarean delivery and often patients are treated as outpatient without narcotic medications [9].

There have been no adequately powered studies to examine whether women that had a cesarean section truly require opioids after leaving the hospital. Performing a comparison between a regimen with NSAIDS (ibuprofen and acetaminophen) and

another combining NSAIDS and an opioid medication (such as hydrocodone), would allow us to stablish prescription guidelines. The knowledge acquired by performing these study, could lead to decreased opioid prescriptions and thus aid in the fight against the national opioid epidemic.

Hypothesis

We hypothesize that there will not be a difference greater than 10mm on pain score measured with visual analogue pain scale at 1-2 weeks and at 4--6 weeks after discharge, among women who have had a cesarean section and are discharged with only a prescription for NSAIDS versus women who are discharged with prescriptions for both NSAIDS and opioids. We seek to determine if NSAIDS alone are equivalent to NSAIDS plus opioids for analgesia after a cesarean section

Objectives

Our primary aim is to determine whether NSAIDS alone can be prescribed after discharge from the postpartum ward without a significant change in pain scores and patient satisfaction in the postpartum period.

RESEARCH DESIGN AND METHODS

Study design

This comparative effectiveness study will be conducted as a randomized, open label, controlled equivalence trial of NSAIDS Vs opioids for management of pain after cesarean section. Previous studies have compared analgesics vs placebo, finding that analgesics are required after cesarean section for pain control [(9)], thus, a comparison against placebo would be unethical and has not been included in the trial design.

Postpartum patients that have had a cesarean section and consent to participate in the study will be randomly allocated to receive either Ibuprofen and acetaminophen or, ibuprofen and acetaminophen plus hydrocodone prior to discharge from the hospital. Currently, opioids are recommended for inpatient analgesia after a cesarean section but there is no standard prescription recommended after discharge from the hospital.

Inclusion criteria

English or Spanish speaker women who had a cesarean section, between 18-50 years old, able to provide consent.

Exclusion criteria

- Inability or refusal to provide informed consent.

- Reported current or prior opioid or benzodiazepine use disorder, including urine drug screen positive for a non prescribed opioid or benzodiazepine upon admission or during prenatal care.

- Current treatment with methadone, buprenorphine or buprenorphine plus naloxone.

- Known alcoholism disorder.

- Severe renal or hepatic impairment.

-Severe peptic ulcer disease

- Severe asthma (if patient has asthma but has previously tolerated NSAIDS, she will be allowed to participate)

- Known CYP450/CY92D6 mutation conferring opioid ultra-rapid metabolizer status.

- Allergy to any of the study drugs (anaphylaxis).

-Incarcerated or institutionalized patients.

- Inability to follow up as outpatient in our outpatient clinic.

- wound dehiscence or infection diagnosed prior to discharge from the hospital

- wound vac placed prior to discharge from the hospital.

Recruitment

Recruitment will occur on the labor and delivery and postpartum wards at Memorial Hermann Hospital-Texas Medical Center. Eligible women will be consented within the 24 hours prior to discharge from the hospital. A member of our research team, either a physician or research assistant/nurse, will obtain written informed consent.

Randomization

Randomization will be performed based on a computer-generated list that will be created by a non-clinical member of the research team. Subjects will be randomized 1:1 to NSAIDS only or NSAIDS and opioids using permuted blocks and stratified by repeat cesarean section (yes/no) and scheduled cesarean section (yes/no). REDCAP, a HIPPA compliant database, will be used for randomization and capture of study data. The randomization sequence will be uploaded in the system. After a patient has consented to be part of the study, pertinent information will be entered in REDCAP and the system will allocate the patient to a research group.

Subjects included in the study will be followed until they stop using analgesics or until 4 -6 weeks postpartum, whatever comes first.

Methods

Patients that have delivered by cesarean section will be approached within 24 hours prior to discharge from the hospital. Immediately after signing the consent form, the patient's information will be input in REDCAP and she will be randomly allocated to either group 1 (prescription for Ibuprofen and acetaminophen after discharge) or group 2 (prescription for ibuprofen, acetaminophen and hydrocodone upon discharge).

Pain level and satisfaction score will be recorded the day of discharge from the hospital along with a brief survey. This will be performed by a trained member of the research team (please see measurement instruments in upcoming sections). In our institution, patients routinely have up to two appointments after discharge from the hospital, one at 1-2 weeks and another at 4-6 weeks. Pain level and satisfaction scores will be recorded during these visits as well, as part of another survey that will also be performed by train research team members. At the time of postpartum outpatient visits, patients will be asked to bring the bottles with their left over medication. The tablets will be counted and handed back to the patient. If a patient does not bring the bottle, she will be asked to tell us the number of pills that she has left over.

If a patient cannot attend the postpartum appointment, she will be contacted via phone to obtain the information from the survey. An email with a link will be sent to record the information from pain scores.

Medication regimen

Patients will be randomized to either group 1 (prescription for Ibuprofen 600 mg po every 6 hours, 60 tablets total after discharge and acetaminophen 500 mg tabs, 1 tablet po every 4 hours, for a total maximum possible daily dose of 3000 mg, 60 tablets total) or group 2 (prescription for same ibuprofen regimen and hydrocodone-acetaminophen (Norco®) 5/325mg tab, one tab po q 4 hours or 2 tabs po q 6 hours, 15 tablets total). All patients will also be given a prescription for 30 tablets of ranitidine150mg tablets, to be taken every 12 hours in case for gastrointestinal upset symptoms. Any physician discharging the patient can write the prescriptions for the study medications.

Please note that the patient's obstetrician will decide which analgesic regimen to order during hospitalization, randomization will be performed prior to discharge and the patient will start these medications at home. The patients will be instructed to take the ibuprofen as scheduled regardless of pain level and only take other medications in case they require additional pain control.

Patients will also be advised that if their pain is not well controlled with the prescribed regimen, they can call the obstetric physician on call for the hospital to obtain a rescue prescription for Norco®.

Primary outcome

Mean pain score, as measured by a visual analog scale and numerical pain scale. We will compare mean scores at discharge, 1-2 and 4-6 weeks postpartum, but our primary outcome will be the score at 1-2 weeks postpartum.

The visual analog scale (VAS) is a widely validated tool, it consists of a 100 mm line, without markups. Patients are instructed to mark a point along the line that represents their pain level, the left hand end of the line represents no pain and the right hand end

of the line represents the worst pain possible. Mean measurements of pain with this tool have been widely described, as well as standard deviations and effect size. The sample size calculation for our study is based on VAS measurements.

Despite the fact that VAS is widely used in research, it is not commonly used in clinical settings, thus, the numerical pain scale has been included, in which 0 means no pain and 10 means the worst pain. This will be an ordinal variable. This scale is commonly used by nurses while patients are in the hospital.

A trained member of the research team will administer a survey and measure pain scores at discharge from the hospital and during the return appointments at 1-2 weeks and 4-6 weeks. Subjects will be asked to record their pain level using both instruments simultaneously. This will provide a good reference for research results application.

As mentioned previously: if a patient cannot attend the follow up appointments, we will attempt to contact her over the phone to administer a survey regarding satisfaction with pain medication regimen and we'll also send an email containing the VAS pain scale so we can obtain this information. If the pain score is not obtained, the patient will be excluded from the analysis.

Secondary outcomes

Maternal:

-Patient satisfaction score: Patients will be asked how satisfied are they with their inpatient analgesics prior to discharged, they will also be asked how satisfied were they with the assigned outpatient analgesic regimen during postpartum appointments at 1-2 weeks and 4-6 weeks. Satisfaction will be measured in a 5 point scale, previously used in our prospective study. The patient will assign a number from the following scale:

Table 1- Satisfaction scale

1	2	3	4	5
Very dissatisfied	Somewhat dissatisfied	Neutral	Satisfied	Very satisfied

Other maternal outcomes include:

- Pain scores measured by visual analogue scale at 4-6 weeks and pain scores measured by numeric scale (0to 10) at 1-2 weeks and at 4-6 weeks

- Number of days of opioid use after discharge from the hospital

- Need for rescue opioid prescription (group 1 only)

- Need for additional opioid refill (both groups)

- Left over medication rate among study groups

- Incidence of side effects: Common side effects expected for Ibuprofen use are: nausea, gastroesophagic reflux, epigastric pain. Common side effects expected from hydrocodone use are: constipation, drowsiness, pruritus, nausea/emesis.

- ER or hospital visit prior to appointment due to incisional pain

Fetal:

-Initiation and continuation of breastfeeding at hospital discharge and during postpartum period.

The information for maternal and fetal outcomes would be obtained by trained research personnel by performing surveys prior to hospital discharge and during postpartum visits. Survey instruments will be attached in a separate document.

Sample size

Sample size calculations are based on VAS score at 1-2 weeks. In prior studies comparing NSAIDS vs opioids, the standard deviation (SD) of VAS scores has been described as 20 mm[20]. In a recent study by Ankumah et al[21], the largest SD described for our patient population was 13.2 mm. In order to perform a conservative sample size calculation, an anticipated SD of 20mm will be used for our study.

Previous studies using VAS have defined a significant effect size to be 10 mm[22]. Thus we would consider NSAIDS alone to be equivalent to opioids if the difference in VAS score is no larger than 10 mm in either direction. We performed an equivalence sample size calculation using an SD of 20 mm, and a difference of 10 mm on the VAS score, 80% power and two-sided alpha of 0.05. A total of 128 individuals would be needed to reject the non-equivalence hypothesis (64 on each study group).

To account for a 30% attrition rate, a total of 184 subjects will need to be recruited, 92on each arm.

Feasibility

Approximately 300 births take place in Memorial Hermann Hospital-Texas Medical Center every month. At a cesarean section rate of 30%, that means that 90 women would potentially qualify for the study every month. Approximately 50% of these deliveries are performed by UTHealth physicians. Private physicians will be approached to inquire whether their patients can be included in this study, in order to perform a conservative calculation, we will assume that only 40 women every month will be candidates for the study.

At a recruitment rate of 50%, 20 women could be enrolled every month and the study would be concluded after 8 months.

Data analysis

Once a patient is randomized into the study, she will be followed and her information collected even if during the study she requires additional analgesics.

Analysis will be performed on the basis of intent to treat. For the primary outcome, we will also perform a per-protocol analysis excluding those patients in NSAIDS only group that required rescue opioid prescriptions. Generalized linear models will be used to analyze all outcomes and will include treatment group and the two stratifying variables, repeat c-section and scheduled c-section, as covariates. For all outcomes we will evaluate the most appropriate distributional form (i.e., Normal, binomial, Poisson, etc) and/or variable transformation. A linear regression model will be used for the primary outcome of VAS score (with appropriate transformation if needed) to estimate the adjusted mean difference and 2-sided 95% CI. Treatments will be regarded as equivalent if the upper bound of the 95% CI is below 10 mm and the lower bound is above -10 mm.

For secondary binary outcomes we will use log binomial models (or robust log Poisson in case of non-convergence) to directly estimate relative risks and 95% CIs. For all other outcomes, we will report 2-sided 95% CIs and p-values. A secondary regression analysis will be conducted for the primary outcome adjusting for parity and drug use.

Bayesian analysis will be performed.

Procedures to Maintain Confidentiality

Data will be kept on paper research charts that will be stored in a locked file cabinet within a locked research office of our research team/research coordinator. In addition, an electronic database of information and data will be stored on the computer of our research coordinator that is password protected, and in a locked office of the research coordinator. The database will be created using REDCAP. Subject information in this database will be de-identified, a linking log will be created in REDCAP as well.

Potential benefits

If we confirm that NSAIDS alone or with a reduced amount of opioids can be used to control postoperative pain after discharge from the hospital, this could potentially change national prescribing guidelines and decrease opioid exposure among postpartum women. This would indirectly contribute to decrease the amount of opioid pills available for potentially misuse across the nation.

Known potential risks

Maternal Side Effects of Opioids

The following table summarizes commonly reported adverse effects of opioids, including hydrocodone [13,14, 25].

Table 2: common side effects of opioid use

Acute Use	Pruritus/Urticaria Nausea/vomiting Constipation Urinary retention Respiratory depression Sedation Delirium Myoclonus Seizures
Chronic Use	Tolerance, dependence and addiction Hyperalgesia Withdrawal symptoms Increased growth hormone secretion Hypogonadism

Maternal side effects of Ibuprofen

Ibuprofen has a short half-life of 2-4 hours and is the preferred analgesic during the postpartum period. Side effects include dyspepsia, heartburn, nausea, vomiting, anorexia, diarrhea, constipation, stomatitis, flatulence, bloating, epigastric pain, and abdominal pain. Peptic ulcer and GI bleeding have been reported [16,24].

Symptoms of overdose include headache, loss of consciousness, tinnitus, CNS depression and seizures. May rarely cause metabolic acidosis, abnormal hepatic function, hyperkalemia, renal failure, dyspnea, respiratory depression, coma, acute renal failure, and apnea (primarily in very young pediatric patients) [24].

Maternal side effects of acetaminophen

Common side effects include nausea, rash and headache. Other side effects are hepatotoxicity, acute tubal necrosis, anema, thrombocytopenia and anaphylaxis[17]

Lactation

Hydrocodone:

Opioids can cause neonatal central nervous system and respiratory depression [23]. Effects are dependent on the amount of opioid transferred in breast milk. In a 2011 report of hydrocodone concentrations in breast milk, Sauberan et[26] al found that breastfed neonates received 1.6% (range 0.2%–9%) of the maternal hydrocodone dose, this is a safe dose for neonates and it has not been associated with adverse neonatal effects.

Theoretically any neonate born to mother that is an ultrarapid metabolizer (UM) could be at risk for opioid toxicity, but no cases of UM and hydrocodone used have been reported in the literature [29].

There are only two reports of adverse neonatal outcomes in mothers that used hydrocodone while breastfeeding, both associated with polymedication: In one report, the mother was taking acetaminophen, fluconazole and hydrocodone simultaneously and reported her neonate slept for most of the day, this symptom resolved after decreasing hydrocodone dose. In the second case the mother used methadone and a combination of hydrocodone with acetaminophen while breastfeeding, her neonate required emergency intubation and no other cause was found for the neonate's respiratory depression [27].

In conclusion, hydrocodone is considered safe during breastfeeding and is one of the drugs currently used for treatment of pain in the postpartum period.

Ibuprofen:

Early studies reported that ibuprofen was not excreted in breast milk[28] however, studies using current technology report that ibuprofen is in fact excreted in breast milk, to a concentration that is <0.38% (0.04%-1.53%) of the weight-adjusted maternal daily dose, which equals 0.2% of the infant dose[29]. Ibuprofen is considered safe during breastfeeding.

Acetaminophen:

The concentration of acetaminophen in breast milk is < 0.1% than that of maternal serum. It is considered safe during breastfeeding [30]

References

1. CDC RUDD: increases in Drug and Opioid Overdose Deaths — United States, 2000–2014Weekly January 1, 2016 / 64(50);1378-82 Rose A. Rudd, MSPH1; Noah Aleshire, JD1; Jon E. Zibbell, PhD1; R. Matthew Gladden, PhD1 On December 18, this report was posted as an MMWR Early Release on the MMWR website (http://www.cdc.gov/mmwr).
2. Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2010–2014. by Margaret Warner, Ph.D., National Center for Health Statistics; James P. Trinidad, M.P.H., M.S., U.S. Food and Drug Administration; Brigham A. Bastian, B.S., Arialdi M. Miniño, M.P.H., and Holly Hedegaard, M.D., M.S.P.H., National Center for Health Statistics. Volume 65, Number 10 December 20, 2016.
3. US department of Health and Human Services. Centers for Disease Control and Prevention. Births: Final Data for 2014, National Vital Statistics Report. Volume 64, Number 12. December 23, 2015. Available at: https://www.cdc.gov/nchs/data/nvsr/nvsr64/nvsr64_12.pdf
4. American Academy of Pediatrics, American College of Obstetricians and Gynecologists. Guidelines for perinatal care. 7th ed. Elk Grove Village (IL): AAP; Washington, DC: American College of Obstetricians and Gynecologists; 2012. p. 109-110, 160, 192-194, 248.
5. Sutton CD, Carvalho B. Optimal Pain Management After Cesarean Delivery. Anesthesiology Clinics. 2016 Dec 12.
6. Prabhu M, McQuaid-Hanson E, Hopp S, Kaimal A, Leffert L, Bateman BT. 817: Shared decision-making for opioid prescribing after cesarean delivery. American Journal of Obstetrics and Gynecology. 2017 Jan 31;216(1):S469.
7. McDonnell NJ, Keating ML, Muchatuta NA, Pavy TJ, Paech MJ. Analgesia after caesarean delivery. Anaesthesia and intensive care. 2009 Jul 1;37(4):539
8. American Academy of Pediatrics, American College of Obstetricians and Gynecologists. Guidelines for perinatal care. 7th ed. Elk Grove Village (IL): AAP; Washington, DC: American College of Obstetricians and Gynecologists; 2012. p. 109-110, 160, 192-194, 248
9. Mkontwana N, Novikova N. Oral analgesia for relieving post-caesarean pain. The Cochrane Library. 2015 Jan 1
10. Osmundson SS, Grasch JL, Schornack LA, Young JL, Lisa ZC, Kelly BA, Michael RG. 704: Opioid use after cesarean delivery following hospital discharge. American Journal of Obstetrics and Gynecology. 2017 Jan 31;216(1):S411-2.
11. Bartels K, Mayes LM, Dingmann C, Bullard KJ, Hopfer CJ, Binswanger IA. Opioid use and storage patterns by patients after hospital discharge following surgery. PloS one. 2016 Jan 29;11(1):e0147972.
12. Bateman BT, Hernandez-Diaz S, Rathmell JP, Seeger JD, Doherty M, Fischer MA, Huybrechts KF. Patterns of opioid utilization in pregnancy in a large cohort of commercial insurance beneficiaries in the United States. The Journal of the American Society of Anesthesiologists. 2014 May 1;120(5):1216-24.

13. Katzung BG, Masters SB, Trevor AJ, editors. Basic & clinical pharmacology. New York, NY, USA: Chapter 31: Opioid Analgesics & Antagonists. Lange Medical Books/McGraw-Hill; 2004 Jan 5.
14. Madadi P, Avard D, Koren G. Pharmacogenetics of opioids for the treatment of acute maternal pain during pregnancy and lactation. Current drug metabolism. 2012 Jul 1;13(6):721-7.
15. Sistonen J, Sajantila A, Lao O, Corander J, Barbujani G, Fuselli S. CYP2D6 worldwide genetic variation shows high frequency of altered activity variants and no continental structure. Pharmacogenetics and genomics. 2007 Feb 1;17(2):93-101.
16. Katzung BG, Masters SB, Trevor AJ, editors. Basic & clinical pharmacology. Chapter 18: Prostaglandins & Other Eicosanoids. Lange 2004.
17. óźwiak-Bebenista M, Nowak JZ. Paracetamol: mechanism of action, applications and safety concern. Acta poloniae pharmaceutica. 2014;71(1):11-23.
18. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e4cfbe12-d712-4ca6-8400-14eec2eca019
19. Reddy UM, Davis JM, Ren Z, Greene MF. Opioid use in pregnancy, neonatal abstinence syndrome, and childhood outcomes: executive summary of a joint workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, American College of Obstetricians and Gynecologists, American Academy of Pediatrics, Society for Maternal-Fetal Medicine, Centers for Disease Control and Prevention, and the March of Dimes Foundation. Obstetrics & Gynecology. 2017 Jul 1;130(1):10-28.
20. Sammour RN, Ohel G, Cohen M, Gonen R. Oral naproxen versus oral tramadol for analgesia after cesarean delivery. International Journal of Gynecology & Obstetrics. 2011 May 1;113(2):144-7.
21. Ankumah NA, Tsao M, Hutchinson M, Pedroza C, Mehta J, Sibai BM, Chauhan SP, Blackwell SC, Refuerzo JS. Intravenous acetaminophen versus morphine for analgesia in labor: a randomized trial. American journal of perinatology. 2017 Jan;34(01):38-43.
22. Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. Emergency Medicine Journal. 2001 May 1;18(3):205-7.
23. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=b165dffd-1550-4d8d-a8ea-fe83512c34e6
24. https://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=all&query=IBUPROFEN&pagesize=20&page=1
25. Gasche Y, Daali Y, Fathi M, Chiappe A, Cottini S, Dayer P, Desmeules J. Codeine intoxication associated with ultrarapid CYP2D6 metabolism. New England Journal of Medicine. 2004 Dec 30;351(27):2827-31.
26. Sauberan JB, Anderson PO, Lane JR, Rafie S, Nguyen N, Rossi SS, Stellwagen LM. Breast milk hydrocodone and hydromorphone levels in mothers using

hydrocodone for postpartum pain. Obstetrics & Gynecology. 2011 Mar 1;117(3):611-7.
27. Hendrickson RG, McKeown NJ. Is maternal opioid use hazardous to breast-fed infants?. Clinical Toxicology (2012), 50, 1–14.
28. Townsend RJ, Benedetti TJ, Erickson SH, Cengiz C, Gillespie WR, Gschwend J, Albert KS. Excretion of ibuprofen into breast milk. American journal of obstetrics and gynecology. 1984 May 15;149(2):184-6.
29. Rigourd V, de Villepin B, Amirouche A, Bruneau A, Seraissol P, Florent A, Urien S, Magny JF, Serreau R. Ibuprofen Concentrations in Human Mature Milk—First Data About Pharmacokinetics Study in Breast Milk With AOR-10127 “Antalait” Study. Therapeutic drug monitoring. 2014 Oct 1;36(5):590-6.
30. Allegaert K, van den Anker JN. Perinatal and neonatal use of paracetamol for pain relief. InSeminars in Fetal and Neonatal Medicine 2017 Jul 15. WB Saunders.

Appendix A: pain scales

Mark a point In the line below that represents your pain level

No pain ——————————————————— worst pain ever

Using the pain scale below, which number would you assign to your current pain level? Please circle answer. 0= no pain, 10= worst pain ever.

0	1	2	3	4	5	6	7	8	9	10