A prospective randomized control trial comparing analgesic benefits of ultrasound-guided single vs continuous quadratus lumborum blocks vs intrathecal morphine for post cesarean section pain

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A prospective randomized control trial comparing analgesic benefits of ultrasound-guided single vs continuous quadratus lumborum blocks vs intrathecal morphine for post cesarean section pain

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III. Study site

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IV. Study Title

Full title-: A randomized control trial comparing analgesic benefits of ultrasound-guided single vs continuous quadratus lumborum blocks vs intrathecal morphine for post cesarean section pain

Running title-: RCT comparing QL blocks, QL catheters vs intrathecal morphine post Csection

V. Study Duration

12 months

VI. Participant patient study duration

Patients will be enrolled from time of admission for cesarean section until post-operative day 3. Total duration of participant enrollment will be for 72 hours.

VII. Trial registration information

XXX

VIII. Clinical Phase

Phase 4

IX. Study significance and background

The rate of Cesarean section (CS) is increasing constantly in the United States (US) and is currently at 31.9 % per the center of disease control and prevention (CDC).("Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Drake P. Births: Final Data for 2016. National Vital Statistics Reports; Vol 67 No 1. Hyattsville, MD: National Center for Health Statistics. 2018." 2018) Post-partum (PP) pain and fatigue is commonly experienced by the women who have delivered via a CS. Severe untreated post-operative CS pain results in increase consumption of opioids, decreased mobility, increased postpartum depression and persistent pain.(Landau, Bollag, and Ortner 2013; Lavand'homme 2013; Kainu et al. 2010)

Single-shot intrathecal morphine sulfate (ITM) injected while performing a spinal anesthetic for CS has been considered the gold standard for post CS pain. ITM provides analgesia for about 14-36 hours. Variable doses of ITM ranging between 50 – 250 micrograms (μcg) have been used. Lower doses of ITM results in fewer side effects however present a tradeoff of shorter duration of analgesia.(Sutton and Carvalho 2017a) Side effects of ITM can be treated with effective prophylaxis and treatment medications. Nalbuphine and naloxone are given to treat pruritus. Nausea and vomiting are treated with ondansetron, metoclopramide, promethazine, and propofol. Respiratory depression is seen with higher doses of ITM (≥ 150 μcg). Patients, who are obese, have obstructive sleep apnea and are on chronic pain medications or patients with opioid tolerance have a higher incidence of respirator depression. Respiratory depression is treated with naloxone bolus followed low dose naloxone infusion. This can antagonize opioid effect and result in pain. Patients with pre-eclampsia receive magnesium, which is sedating and can further cause respiratory depression.(Sutton and Carvalho 2017a) The bimodal respiratory depression associated with ITM requires intense monitoring of respiratory status for the first 24 hours and special training for providers caring for these patients.

Eighty-one percent of all women in the US initiate breast-feeding (BF) postpartum. Early BF improves maternal-neonatal bonding. Effective pain control promotes successful BF.

A relative infant dose (RID) expressed as a percentage and is weight adjusted for the neonate (Table 1). It quantifies the amount of neonatal drug exposure relative to the mother's dose. A value of greater than 10% is considered high. (Sutton and Carvalho 2017b) Highly protein bound drugs like non-steroidal anti-inflammatory drugs (NSAID's) and local anesthetics (LA) have limited transfer to the neonate.

Acetaminophen provides effective analgesia PP with minimal side effects as a part of the multimodal analgesia plan (MPP). It has an opioid sparing effect of approximately 20%.

Scheduling acetaminophen for 2-3 days post CS has been recommended.(Bollag et al., n.d.)

Ibuprofen has a short half-life. RID is 0.6% in colostrum and <0.38% in mature milk. This is equivalent to 0.2% of the pediatric dose. Scheduled ibuprofen for 2-3 days has also been recommended in addition to scheduled acetaminophen. (Bollag et al., n.d.)

Table 1: Relative infant dose for different medications

Drug	**Relative infant dose**
Acetaminophen	1.3-6.4
Ibuprofen	0.1-0.7
Ketorolac	0.2-0.4
Celecoxib	0.3
Gabapentin	1.3-6.5
Hydrocodone	1.6-3.7
Oxycodone	1.5-8
Tramadol	2.4-2.9
Fentanyl	0.9-3
Morphine	5.8-10.7

The quadratus lumborum block (QLB) was initially described by R. Blanco.(Blanco, Ansari, and Girgis 2015) This block covers not only the somatic innervation of the body wall, but also provides relief of visceral pain. Given its versatility, the quadratus lumborum block has successfully been used in a wide range of procedures including gastrectomies, colectomies, prostatectomies, nephrectomies, cystectomies, cesarean sections and hysterectomies.

There are three types of quadratus lumborum blocks: quadratus lumborum type 1 (QLB1), quadratus lumborum type 2 (QLB2) and trans-muscular quadratus lumborum block (TQLB). For all three blocks, the needle enters the lateral abdomen near the posterior axillary line, below the costal margin and above the iliac crest. In QLB1, the anesthetic agent is injected into the potential space medial to the abdominal wall muscles and lateral to the quadratus lumborum muscle (QL). This block covers the dermatomal

area from T10 to L1, and is typically used for abdominal surgeries being conducted below the umbilicus. In QLB2, the anesthetic agent is injected just posterior to the QL muscle and covers T4 to L1. The QLB2 block effectively blocks the anterior and lateral cutaneous branches of the nerves. It is typically used for abdominal surgery either above or below the umbilicus (any type of operation that requires intrabdominal visceral pain coverage and abdominal wall incisions as high as T6). In TQLB, the anesthetic agent is injected anterior to the QL muscle, between the QL and the psoas major muscles. This block has analogous coverage to the QLB2 block and thus has the same clinical indications as the QLB2 block. However, this block is more difficult to perform than the QLB2 block, and can result in quadriceps weakness due to spread to the lumbar plexus on the anterior surface of the psoas major muscle. (Ueshima, Otake, and Lin 2017)

Early oral intake, mobilization, removal of urinary catheter are all important components of the enhanced recovery after surgery protocol (ERAS). We hypothesize that by performing QL blocks post CS the amount of pain, narcotic consumption will be reduced significantly. Early ambulation will help prevent deep vein thrombosis. Performing QL blocks will also minimize side effects secondary to ITM and will facilitate ERAS and better patient satisfaction scores.

A recent study conducted by Salama et al concluded that QLB (without ITM) provided lower numeric rating scores at rest and during movement when compared to the group that received ITM (without QLB). Time to first morphine dose was also longer in the QLB. This study concluded that a longer duration of analgesia and reduced postoperative morphine consumption was achieved with QLB when compared to ITM.(Salama 2019)

X. Sample size

25 in each group

Total number of enrolled patients: 75

XI. Study population

Inclusion criteria

1. Age greater than 18 years
2. Elective C section via Pfannenstiel incision
3. Living singleton pregnancy
4. Gestation week at least 37 weeks
5. ASA status 1, 2 and 3

6. Primary and secondary C sections

Exclusion criteria

1. Chronic pain
2. Opioid tolerant patients
3. Allergy to drugs used in the study.
4. Cognitive dysfunction
5. BMI > 40
6. Coagulation disorder
7. Local infection
8. Inability to tolerate oral medication
9. Previous intra-abdominal surgery
10. Patients who will receive a combined spinal epidural for their C section
11. Local anesthetics injected at any other fascial plane except the QLB plane (for e.g.- local wound infiltration by surgeon)
12. Patients who received sedation or general anesthesia during their CS (midazolam, ketamine, fentanyl, propofol, hydromorphone)

Voluntary patient withdrawal from the study- patient has right to withdraw at any point during the study period

Withdrawal in case of unexpected events- This will be determined by the investigators.

XII. Primary objective

Primary objective of the study is to compare opioid consumption in morphine equivalents between the groups that received postoperative analgesia with intrathecal morphine versus US guided QL blocks versus US guided QL catheters

Our working hypothesis is-

1. Single shot QL block is equivalent to intrathecal morphine with less side effects in providing post-operative pain control for the first 24 hours.

2. Continuous QL catheter is more beneficial than single shot QL block or intrathecal morphine after 24 hours in providing post-operative pain control.

3. Our exploratory hypothesis is that after 48 hours a QL catheter would continue to reduce morphine consumption until 72 hours.

Primary outcome measure

Total narcotic consumption in morphine equivalents (in milligrams) for the first 72 hours after surgery will be calculated. Total narcotic used in the spinal anesthetic will be excluded.

XIII. Secondary objectives

1. Total narcotic usage at 24 and 48 hours will be assessed in morphine equivalents. Intraoperative consumption of opioids will be excluded.

2. Time to first analgesic request

3. Numeric pain score (NPS)- static and dynamic at 6, 12, 24, 48 and 72 hours

4. Pruritus at 24, 48 and 72 hours

5. Nausea at 24, 48 and 72 hours

6. Vomiting at 24, 48 and 72 hours

7. Sedation at 24, 48 and 72 hours

8. Patient satisfaction- quality of sleep, ability to ambulate, and ability to breast feed and take care of newborn at 24, 48 and 72 hours

Secondary outcome measures-

1. Total narcotic consumption in morphine equivalents (in milligrams) at 12, 24 and 48 hours will be measured.

Time after CS	Total morphine equivalents (mg)
At 4 hours	
At 6 hours	
At 12 hours	

At 24 hours	
At 72 hours	

2. Time to first analgesic request will be reviewed from the chart

3. Our research personnel will use NPS. This will be assessed at 6, 12, 24, 48 and 72 hours. NPS is a 11-point scale as shown below. The study patient will verbally select a numerical value that best corresponds with the pain the patient is experiencing at that point. This data will be statistically analyzed. Static and dynamic pain scores will be assessed. Dynamic pain scores will be assessed by asking the patient to sit up in bed from supine to sitting at 6 hours. This will be repeated at 12, 24,48 and 72 hours however if patient is ambulating, dynamic pain score during ambulation will be assessed.

No pain Distressing pain Worst pain

No pain (0) Mild pain (1,2,3) Moderate pain (4,5,6) Severe pain (7,8,9,10)

Time interval after CS	**NPS (static)**	**NPS (dynamic)**
At 6 hours		
At 12 hours		
At 24 hours		
At 48 hours		
At 72 hours		

4. Numeric scale to rate side effects (SE) of pruritus, nausea, vomiting and sedation at 24, 48 and 72 hours; 0- no side effects 10- extremely severe side effect possible. This numeric scale is a 11-point scale as shown below. The study patient will verbally select a numerical value that best corresponds with the side effects the patient is experiencing at that point. This data will be statistically analyzed.

No SE Distressing SE Worst SE

No SE (0) Mild SE (1,2,3) Moderate SE (4,5,6) Severe SE (7,8,9,10)

Side effects	**Scale at 24 hours**	**Scale at 48 hours**	**Scale at 72 hours**
Pruritus			
Nausea			
Vomiting			
Sedation			

5. Patient satisfaction will be measured on a Likert scale (5 points) at 48 and 72 hours. How satisfied were you with the following?

	Extremely satisfied	Very satisfied	Moderately satisfied	Slightly satisfied	Not satisfied
Quality of sleep					
Ability to ambulate					
Ability to breast feed/ formula feed					
Ability to take care of new born					

XIV. Study drugs

1. Preservative free morphine
2. Normal saline
3. Bupivacaine hydrochloride 0.25 %
4. Ropivacaine hydrochloride 0.1 %

XV. Study schedule

Expected start date for enrolling patients

Expected end date for enrolling patients

Enrollment period for each patient- 72 hours, earlier if discharged.

XVI. Study design

This is a prospective double-blinded randomized control trial performed at a single institution.

Screened patients meeting inclusion criteria will be randomized into three groups:

Group 1- Spinal anesthesia with ITM + US guided QLB single shot sham block + QLB catheters with no continuous infusion

Group 2- Spinal anesthesia without ITM + US guided QLB single shot with bupivacaine hydrochloride + QLB catheters with no continuous infusion

Group 3- Spinal anesthesia without ITM + US guided QLB single shot with bupivacaine hydrochloride + QLB catheters continuously infusing 0.2% ropivacaine hydrochloride

Placement of spinal anesthesia- This will be performed by the attending anesthesiologist or anesthesiology resident who are providing anesthesia for the patient in the operating room. The anesthesia technique will be standardized. A spinal anesthetic will be performed in the sitting position at the lumbar vertebra level (L) either at L3-L4 or L4-L5 level. All women will receive a spinal anesthetic using 0.75% hyperbaric bupivacaine 912 mg plus fentanyl 20 micrograms plus epinephrine 1:100,000 100 micrograms administered intrathecally. The anesthesiologist caring for the patient will not be blinded. The anesthesiologist caring for the patient will open an opaque envelope handed to him/her by the research personnel. The envelope will clearly state the group the patient is assigned to and if ITM 200 micrograms should be added or excluded from the spinal medication. Spinal block efficacy will be considered successful if a sensory block to pinprick is achieved at a level of thoracic (T) 6 or higher. Anesthesia and surgery will be performed in the usual manner.

Placement of QL blocks- Immediately after wound closure, bilateral QL blocks will be placed by one of the investigators under direct ultrasound guidance (Sonosite X-Porte, Sonosite, Bothell, WA). For the purpose of our study we will be utilizing the QL 2 technique by Blanco to achieve blockade from T7-L1 dermatomes.(Blanco et al. 2016; Blanco, Ansari, and Girgis 2015) The anesthesiologist caring for the patient will open the opaque envelope and prepare the study drug. The study drug will either be a sham 20 ml empty syringe or 0.25% bupivacaine hydrochloride 20 ml each side. The patients will be in the supine position with a small roll of blanket placed under the ipsilateral flank. The abdomen will be cleaned with 2 % chlorhexidine gluconate and 70 % isopropyl alcohol solution (ChloraPrep® One-Step). If the patient has an allergy to any of the contents of

the cleaning solution, 10% Povidone-Iodine solution will be used. The ipsilateral abdomen will be draped with sterile towels. A transverse linear array probe (HFL50 6-15 MHz) placed in a sterile probe cover with an imaging depth of 4-6 cm will be placed at the level of the anterior superior iliac spine and moved cranially until the three abdominal muscles are identified; external oblique (EO), internal oblique (IO), transverse abdominis (TA). The EO muscle will be followed posterior and laterally until its posterior border is visualized. The IO muscle should come into view overlying the QL muscle. The probe will be tilted to identify a bright hyperechoic line that corresponds to the middle layer of the thoraco-lumbar fascia. An 18 G echogenic peripheral nerve block needle (Contiplex® Ultra 360™ continuous nerve block set, B Braun, Bethlehem, PA, USA) will be inserted in plane from anterolateral to posteromedial direction. The optimal point of injection for the QL will be determined by hydro dissection with normal saline. Primary block will be performed depending on the group allocation of the patient. The patient will receive either no drug (Group 1) or bupivacaine hydrochloride (Group 2 and Group 3). QL catheters will be placed as described below. A QL2 block will be performed on the contralateral side in a similar fashion.

Placement of QL catheters- A 20 G peripheral nerve polyamide catheter (Contiplex® Ultra 360™ continuous nerve block set, B Braun, Bethlehem, PA, USA) will be inserted through the 18 G echogenic needle under direct ultrasound visualization. The catheter will be secured using the standard technique employed at our institution. Correct placement of QL catheters will be confirmed by injecting saline under ultrasound guidance. QL catheter will be placed on both sides in a similar fashion. A member of the research team who performed the initial QLB in the operating room will attach a peripheral nerve pump (CADD® Solis ambulatory infusion pump, Minneapolis, MN, USA) to the QL catheter once the patient reaches the post anesthesia care unit (PACU). No infusion will be initiated if the patient is assigned to group 1 (Spinal anesthesia with ITM + US guided QLB single shot sham block + QLB catheters with no continuous infusion) and group 2 (Spinal anesthesia without ITM + US guided QLB single shot with bupivacaine hydrochloride + QLB catheters with no continuous infusion). Infusion of 0.2 % ropivacaine at 10 ml/hour on each side will be initiated if the patient is randomized to group 3 (Spinal anesthesia without ITM + US guided QLB single shot with bupivacaine hydrochloride + QLB catheters infusing 0.2% ropivacaine hydrochloride). A member of our research team who is blinded to the group allocation will manage all peripheral nerve catheters. No extra bolus medication will be given through any of the catheters. We are not initiating any infusion through the peripheral nerve catheters in group 1 and 2 to avoid the possibility of pain due to stretching of muscles and facial planes by normal saline.

All patients will be started on a multimodal pain regimen. They will receive scheduled acetaminophen 1000 mg orally and ibuprofen 600 mg every 6 hours. Oxycodone 2.5 mg-5 mg oral every 4 hours as needed will be added for breakthrough pain. Patients will be

evaluated by the anesthesia pain service for adding a PCA with intravenous hydromorphone if pain not adequately controlled on their regimen.

Our research personnel who will be blinded, will follow up patients for the first 48 hours to collect data listed under primary and secondary objectives. We are not assessing dermatomal levels to determine the spread of local anesthetic as it could possibly result in patients and study personnel knowing which group they fall under and potentially unblinding the study.

XVII. Conduct

1. Screening

   Our research team will assess patients for eligibility based on the inclusion criteria. We will obtain informed written consent from all eligible patients. Any member of our research team at any point will obtain this consent during the preoperative period (anesthesia clinic, surgery clinic, preoperative holding area). Patients will be given adequate time to consult with family members and use the internet for additional information. All questions and concerns by the patient will be addressed at this point.

   Once a written informed consent is obtained the patient will be educated about the study protocol, NPS assessment, other assessment tools and the use of MMP medications. Baseline pain score will be recorded at this point. A complete preoperative evaluation, physical examination and preoperative testing will be conducted per usual protocol by the anesthesiologist caring for the patient.

   Three copies will be made of the written informed consent. Patient will be given a copy of the signed written informed consent. A copy of the consent will be placed in the patient's chart. Our research team will keep one copy of the consent.

2. Enrollment

   Patient will be enrolled if all inclusion, exclusion criteria are met and the patient has provided an informed written consent. Our research coordinator will then randomly assign the patient into one of the groups based on the random allocation software.

3. Randomization and allocation concealment

   Anesthesiologist in the operating room will not be blinded to the patient's randomization, as they must prepare the spinal with or without intrathecal morphine and the prescribed solution for block placement. Anesthesiologist performing the regional nerve block not be blinded as they will have to perform a

sham QLB or a QLB with the study drug. All other research personnel collecting data or seeing the patient postoperatively will not know what the contents of the spinal medication were, whether or not the QLB contained no drug or bupivacaine, or whether the QLB catheter infusions contain no drug or ropivacaine.

Patient's assigned group will be communicated to the anesthesiologist caring for the patient in an opaque envelope so that no other research personnel are wise to the assignment.

Research personnel responsible for randomizing and assigning group will not be the same personnel as those evaluating the patient or collecting data.

4. Preoperative assessment

A complete pre-operative assessment will be done by the anesthesiologist or resident physician caring for the patient. Our research personnel will only evaluate patient to verify if they meet our inclusion criteria.

5. Follow up

Our research personnel who will be blinded to the study drugs used, will follow up patients.

Following data will be collected from the patient at the following time intervals.

At 6 hours	NPS		
At 12 hours	NPS		
At 24 hours	NPS	NRS for SE	
At 48 hours	NPS	NRS for SE	Likert scale for patient satisfaction

6. Termination of enrollment

Enrollment will be terminated if the following criteria are met-

i. At the end of the 48-hour period

ii. Intraoperative complication resulting in post-operative prolonged ventilation

iii. Failure of neuraxial spinal anesthesia or conversion to general endotracheal anesthesia during the C section

iv. Pfannenstiel incision converted to any other type of incision during surgery

v. Patient death within 48 hours vi. Termination of study

7. Termination of study

After data collection, analysis and publication of results.

XVIII. Adverse event reporting

All patients will be monitored for adverse events. Adverse events if any will be duly documented in the research file as well as in the patient's medico legal record. All adverse events will be reported to the data safety monitoring board (DSMB). The patient will be informed of all adverse events such as local anesthetic systemic toxicity, local infection, bleeding.

XIX. Sample size and statistical analysis

Size consideration:

Based on preliminary data collected on 12 patients receiving intrathecal morphine at our institution, the mean consumption in morphine equivalents are 27 (SD=25), 29 (SD=23) and 11 (SD=10) for 24 hours, 24-48 hours and 48-72 hours, respectively. Significance level 0.05 and two-sample t test are used for all size calculations. **Working hypothesis 1**: One patient receiving single shot QL block did not consume morphine within 24 hours. We conservatively use 10 as the mean for single shot QL block. Using a one-sided t-test, single shot QL block would be considered as non-inferior to intrathecal morphine if $\mu_S\mu_I<\delta$, where δ is the non-inferiority margin. Given SD=25, for δ=5, 23 patients per group provides the power of 90% for confirming non-inferiority. **Working hypothesis 2:** Based on preliminary data of morphine consumption in 24-48 hours, one patient receiving continuous QL catheter consumed 20 and one patient receiving single shot QL block consumed 49. We use 20 and 49 as mean consumptions of these two arms with SD 23. Based on a two-sided t-test, the size of 15 per group provides the power of 91.5% for detecting significant lower amount of consumption for continuous QL catheter. **Final size and power**: We aim at confirming both hypotheses 1 and 2 with type I error 5%. The overall power is probability of confirming both hypotheses given the aforementioned means (as well as SD's) for these three arms. We set the target enrollment to be 23 per group. The overall power for this size is estimated to be 89.4% based on simulation of 10000 replicates, assuming independence between tests of hypotheses 1 and 2. We compensate the drop-out by inflating the size to 25 per group.

Statistical analysis plan:

The data will be analyzed within one month after completion of data collection for all enrolled patients. The deidentified data will be uploaded to PI's UTH-Share account and shared with the statistician. We will conduct Kolmogorov–Smirnov test to test normal distribution. Continuous variables will be summarized as mean and standard deviation for each group. Comparisons between any two groups will be evaluated by two-sample t test. If a variable has skewed distribution, we will report median and inter-quartile range and use Wilcoxon rank sum test for two-sample comparison. Incidences of side effects and patient satisfaction scales will be summarized as frequency and percentage for each group. Their association with intervention arm will be evaluated by Fisher's exact test. P values less than 0.05 will be considered as significant. Test and confidence interval are equivalent methods. SD is needed in calculating a confidence interval. The test is equivalent to obtaining a 90% confidence interval and comparing the upper limit of confidence interval to δ. All statistical analyses will be performed by using the SAS software (version 9.4, the SAS Institute, Cary, NC).

XX. Ethics

1. Informed consent- An informed, voluntary consent will be obtained systematically. Once the patient meets inclusion criteria, a member of our research team will speak with the patient about the study. Information will be provided regarding all study drugs, intervention and post-operative care. Standard treatment options will also be provided. Adequate time will be provided so that the patient can consult with family members, friends or look up more information using the internet.

2. Privacy and confidentiality- The patient will be linked with a study number. Only specific computers will be used by our research team to store patient information. All data will be restricted to team members, institutional review board (IRB) and FDA. Health insurance portability and accountability act (HIPPA) will be strictly followed.

3. Risk vs benefits- Major risks involved with this study are unintentional disclosure of patient information and adverse effect due to the local anesthetic leading to LAST. There is no monetary benefit involved with this study. Patient will benefit from adequate pain control with this intervention.

XXI. Study timeline

Recruitment of sample size- 9 months

Data collection and analysis- 3 months

No long-term follow up is needed with this study.

Results will be published at the end of data analysis.

XXII. Data safety monitoring

All drugs are FDA approved for the indication being used for.

XXIII. Conflict of interest

No conflicts of interest

XXIV. Publication

Study results will be submitted as a poster at an international conference and will be published in a peer-reviewed journal.

XXV. Funding

I have applied for funding through the Clinical Research Grant through the UTHealth Department of Anesthesiology.

XXVI. Abbreviations

QL- Quadratus lumborum block

CS- Cesarean section

ITM- Intrathecal morphine

µcg- Micrograms

ASA- American Society of Anesthesiologist

MMP- Multimodal analgesia plan

NPS- Numeric pain scale

NRS- Numeric rating scale

VAS- Visual analogue scale

PCA- Patient controlled analgesia

PP- Post partum

BF- Breast-feeding

US- United States

NSAID's- Non-steroidal anti-inflammatory drugs

LA- Local anesthetics

LAST- Local anesthetic systemic toxicity

DSMB- Data safety monitoring board

FDA- United states food and drug administration

IRB- Institutional review board

HIPPA- Health insurance portability and accountability act

XXVII. References

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