Patient-controlled Analgesia with Remifentanil in a Parturient with Ankylosing Spondylitis and SARS-CoV-2 Infection: A Case Report

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ABSTRACT

Parturients with both ankylosing spondylitis (AS) and SARS-CoV-2 Infection (COVID-19) present unique challenges to anesthesiologists. Neuraxial analgesia for labor remains the gold standard in obstetric patients. However, in patients with AS, this approach may be deemed difficult to impossible. Administration of systemic opioids for labor analgesia can be an option, bearing in mind the potential respiratory depressant effect to both the mother and the fetus, especially in the setting of concomitant COVID-19. This paper reports the successful management of such a patient using patient-controlled analgesia (PCA) with intravenous remifentanil.

Keywords: ankylosing spondylitis, remifentanil, patient-controlled analgesia, obstetric analgesia, COVID-19

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INTRODUCTION

Ankylosing spondylitis, an axial form of arthritis, is a rare but well-established cause of chronic back pain. The primary sites of involvement are the sacroiliac joints and the spine, progressing cranially. In its more advanced states, fibrosis and calcification result in the loss of flexibility and fusion of the spine, resembling an immobile "bamboo" configuration.[1,2] As the peak incidence is in the young adult population, it is not uncommon to have pregnant patients with this coexisting condition.

Neuraxial analgesia (NA) has remained the "gold standard" for parturients in labor due to its superior analgesic effectiveness compared to systemic opioids as well as its minimal impact on neonatal respiratory status. However, skeletal deformities such as in AS present as relative contraindications to neuraxial anesthesia. Needle placement may be difficult and the spread of medications in the epidural space may be unpredictable or limited due to the anatomic alterations such as ossification of spinal ligaments and reduced intervertebral spaces.

Alternatives to NA to manage labor pains include inhaled nitrous oxide (N_2O) and opioids administered intramuscularly or intravenously. Recently, remifentanil, an ultrashort-acting synthetic opioid with favorable maternal and fetal pharmacokinetics, has become an alternative opioid via patient-controlled analgesia (PCA). Although less effective compared to NA, remifentanil PCA has shown distinct advantages over N_2O, pethidine, and fentanyl, and has been shown to be an effective analgesic for labor with good maternal satisfaction ratings.[3]

The management of parturients with COVID-19 should take into consideration possible respiratory complications to the mother including pneumonia, respiratory failure, and acute respiratory distress syndrome, and possible effects to the newborn due to placental or droplet transmission.[4] Adverse effects of remifentanil include respiratory depression, hypotension, bradycardia, and muscle rigidity sufficient to compromise breathing.[5] Giving this drug to parturients with COVID-19 must be done with caution as rapid clinical deterioration can occur in symptomatic pregnant women.

As the guidelines for use of remifentanil PCA for labor analgesia remain mostly institutional recommendations and are not standardized, this case describes the use of remifentanil as an alternative option for labor analgesia in a COVID-19 positive parturient with ankylosing spondylitis.

CASE PRESENTATION

A 35–year-old, ASA 2, pregnant woman, G3P1 (1011) presented at the Philippine General Hospital Obstetric Admitting Section for labor pains on her 38th week of gestation.

The patient had a 16-year history of on and off bilateral hip pain. She was formally diagnosed with Ankylosing Spondylitis (AS) by a rheumatologist three years prior to the present pregnancy upon findings of chronic and active inflammatory arthropathy in the Magnetic Resonance Imaging (MRI) of her lumbosacral spine and sacroiliac joints, and serological tests showing positive human leukocyte antigen B-27 (HLA-B27) and elevated Erythrocyte Sedimentation Rate (ESR). She was managed with anti - Tumor Necrosis Factor (TNF) alpha infusions (Infliximab), non-steroidal anti-inflammatory drugs (Celecoxib), and paracetamol which intermittently afforded relief of her symptoms which included chronic fatigue, difficulty sleeping, back pain on lying supine, pain and stiffness of the small joints of her hands, occasional "popping" of the temporomandibular joint (TMJ), and difficulty with lateral head turning.

Her first pregnancy 11 years PTA was carried to full term and she underwent normal Spontaneous Vaginal Delivery (SVD) without labor analgesia. She reported no difficulty assuming the lithotomy position for delivery despite her hip pain. Her 2nd pregnancy four years PTA resulted in a miscarriage at 10 weeks age of gestation. She was in treatment for uveitis at that time with topical ophthalmic anti-inflammatories and took no other systemic medications. No further work-up was done for the pregnancy loss.

The patient had complete vaccination as per the Expanded Program of Immunization as well as two COVID-19 vaccines and one booster dose.

Pertinent family history included two uncles on her maternal side who also exhibited severe arthritis (one developing marked thoracic kyphosis and one with unremitting hip pain) but were never formally diagnosed by a physician.

The patient sought admission upon onset of labor. Reverse transcription-polymerase chain reaction (RT-PCR) test done per hospital protocol showed a positive SARS-CoV-2 Infection (COVID-19). Despite the absence of respiratory signs and symptoms, she was isolated and provided with oxygen supplementation per protocol. Standard monitors (NIBP, pulse oximeter, and electrocardiogram) were attached. Internal exam showed 5-cm cervical dilatation, station -3, with moderate to strong contractions every 2-3 minutes, NRS 10/10 during the peak of contraction.

Pertinent physical examination findings included: BP 130/80 mm Hg, HR 90 bpm, RR 16 cpm, SpO_2 99%, and BMI of 35 (weight: 80 kg, height: 150 cm). Airway examination revealed: Mallampati 1, two finger breadth mouth opening, thyromental distance of 5cm, no limitation on neck flexion and extension but limited lateral rotation of the cervical spine (about 30 degrees on both directions), and stiff paracervical muscles. Chest and lung findings were normal. Abdominal findings were consistent with her gravid state. Neurological examination revealed no sensorimotor deficits.

Focused examination of her spine and back showed normal cervical and thoracic curvatures. In her lumbar area, there was note of stiff, non-tender paraspinal muscles with resulting loss of lumbar lordosis. When asked to assume the fetal position while lying on her side, there was limited spine flexion. There was no noted limitation of hip and knee range of motion.

After careful review of her history and current disease status, the anesthesia and obstetrics team discussed with the patient the options for labor analgesia. Neuraxial analgesia could be attempted but it might take a longer time than usual to insert the epidural and its effectiveness was not guaranteed. PCA IV opioids including remifentanil were discussed including the possible respiratory effects to the mother and the baby. As the patient was in active labor already, she verbalized preference for the fastest pain relief and consented for intravenous analgesia instead of neuraxial analgesia.

To provide labor analgesia, intravenous (IV) remifentanil PCA was initiated using a syringe pump with PCA bolus capabilities (B. Braun Perfusor® Space). This syringe pump can deliver a bolus in 1-3 seconds. One mg of remifentanil was mixed with 49mL of PNSS to make a 20 µg/mL of solution. PCA settings were: a bolus dose of 1 mL (20 µg) and a lockout period of three minutes with a 1-hour limit of five doses. There was no background infusion. A dedicated IV line (1L PNSS to run at 20 cc/hr) was inserted in the patient's right metacarpal vein for the PCA.

In the labor room, oxygen supplementation and standard monitors were maintained. An OB resident was tasked to monitor the patient closely for an hour upon initiation of PCA to assess the PCA's effectiveness. The vital signs were taken every 15 minutes with emphasis on monitoring for signs of respiratory depression, desaturation, and bradycardia.

The OB resident, nurses, and medical interns then took turns monitoring the patient until she delivered.

The patient was instructed to press the PCA bolus button at peak uterine contractions. She had a total of seven bolus administrations in the first two hours of PCA (approximately 15 minutes apart). There was notable decrease of pain scores from NRS 10/10 to 5/10 after administration of each remifentanil boluses. As labor progressed, however, contractions became stronger and more frequent. NRS remained 8/10. Hence, the remifentanil bolus dose was increased to 2 ml (40 μg) and lockout period decreased to 2 minutes, still with no background infusion. The patient had two PCA bolus doses until she delivered 30 minutes later. Local anesthesia infiltration with lidocaine 2% was administered at the episiotomy site upon fetal crowning. The patient successfully delivered via spontaneous vaginal delivery a live baby girl APGAR 9,9 with birthweight appropriate for gestational age (AGA). Intravenous paracetamol 1g and ketorolac 30 mg were given for postpartum analgesia. During the entire labor analgesia and vaginal delivery, the patient had normal vital signs and had no decreases in sensorium nor desaturation. Both the mother and the neonate had an uneventful postpartum course and were discharged home three days later.

DISCUSSION

Ankylosing spondylitis has a global prevalence of approximately 7.4-31.9 per 10,000 individuals, with the Philippines having the least reported cases in Southeast Asia at around 3 per 10,000.[6] Pregnancy complicated by AS has rarely been reported in our country. AS is most frequently seen in the third or fourth decade of life, with a 3:1 male to female ratio. The symptoms of AS usually start between 15 and 30 years of age but confirmation of AS can be delayed by many years, much like in our index patient.[7] In our patient, the diagnosis of AS was established with the progressive nature of her symptoms, starting with pain in the hip joints, then pain and limited motion in the lower back, to extra-axial skeleton manifestations such as hand joint stiffness and pain, TMJ dysfunction, and uveitis. MRI findings of sacroiliitis and lumbar vertebrae acute and chronic inflammatory and osteophytic changes further confirmed the diagnosis.

An early study in the 90's had shown that AS did not adversely affect fertility, pregnancy outcome, or the neonate with delivery occurring at term in 93.2% of cases.[8] More recent studies, however, have shown that AS alone[7] or belonging as a subgroup of axial spondyloarthritis (axSpA)[9], have shown a higher prevalence of complications in pregnancies overall - including preterm birth, preeclampsia, and low birth weight when compared to the general population. Miscarriage has also been shown to be high (16.7%) in AS patients who became pregnant.[9] With this information, disease control prior to conception should be encouraged to increase the chances of a successful pregnancy. Our patient had an unremarkable first pregnancy but her second one ended in a miscarriage. She had severe symptoms at that time and was even undergoing uveitis treatment which could have contributed to the pregnancy's poor outcome. A history of medication such as NSAID's, steroids, and disease-modifying antirheumatic drug (DMARD) to control AS has been shown to increase risk of preterm birth.[7] Prior to her current pregnancy, she was able to undergo four sessions of Infliximab infusions which greatly reduced her flares and symptoms, an indication of better disease control. Her medications were also temporarily discontinued prior to her conception, reducing her risk for fetal complications.

Ankylosing spondylitis as a chronic, progressive, multisystemic disease, can present unique challenges to the anesthesiologist whether performing general anesthesia (GA) or regional anesthesia (RA). Advanced disease states can complicate administration of GA as aside from a difficult airway (limited neck mobility and TMJ dysfunction), patients can have pulmonary (restrictive physiology), cardiac (valvular and conduction abnormalities), gastrointestinal, and nervous system issues. Administration of neuraxial anesthesia can be complicated by lumbosacral spine abnormalities including narrowed spinal canal (unpredictable spread of LA) and spine segment stenosis and/or fusion (impossible needle or catheter placement). Our patient presented with features of limited mouth opening, TMJ dysfunction, and restricted lateral neck movement which could have made airway management difficult. She had extra axial manifestations of AS such as arthropathy in her hands and uveitis but her chest and lung findings were normal. Examination of her back showed limited lumbar flexion which could have been challenging but not impossible for catheter placement for labor analgesia or administration of spinal anesthesia for cesarean section.

Pregnancy complicated by AS is rare and so are the reported anesthetic technique for labor pain management and vaginal delivery, as well as abdominal delivery. Regardless of the technique, special assessment is required as patients can have risk factors for both GA and RA. Also, a planned vaginal delivery can unexpectedly be converted to an abdominal delivery. It is strongly recommended for parturients with AS to have a trial of labor as operative delivery may be technically difficult for both obstetrical and anesthesia-related considerations and may contribute to postoperative cardiopulmonary complications. As such, adequate preparations and planning should be made for abdominal delivery under GA, and the operating room prepared for a difficult airway scenario.[10]

Most pregnant women with AS go to term gestation with vaginal deliveries with or without labor analgesia. The incidence of abdominal deliveries (cesarean section) has been shown to increase among AS patients, with factors including a more severe AS phenotype as reflected by a more extensive medication, certain comorbidities and pre-eclampsia as contributing factors.[7] It has been suggested that

spinal anesthesia can be safely and effectively used instead of GA for parturients with AS.[11] Our patient was admitted for term pregnancy and in active labor already hence, the obstetricians planned for vaginal delivery. She already had a previous term pregnancy delivered vaginally, so the plan was to do the same. She had no known co-morbidities such as diabetes or hypertension before and during her pregnancy. There was also no perceived difficulty in vaginal delivery (bony pelvic prominences, abnormal fetal presentation) nor difficulty placing the patient in a dorsal lithotomy position (hip and knee joint restrictions).

The provision of labor analgesia to parturients with AS has been approached several ways. A large population-based study in Sweden showed that the use of epidural analgesia (26.5%) in pregnant patients with AS was comparable to that in their general population (26.2%), although the final outcome, whether vaginal or abdominal delivery was not mentioned.[7] A report of a patient with severe AS has shown that a successful epidural catheter placement does not guarantee effective labor analgesia. The postulated reason was that the rostral spread of the local anesthetic was limited by the calcified posterior longitudinal ligament. Instead, continuous spinal anesthesia was utilized for labor analgesia.[10] Even though neuraxial analgesia (epidural and combined spinal-epidural) remains the gold standard among parturients in labor, several options including inhaled nitrous oxide (Entonox), intramuscular opioids, and intravenous opioid via patient-controlled analgesia have become available to patients. Despite the advantages of neuraxial analgesia, there may be contraindications to its use in some women. Patient choice regarding use of NA or not, and the use of alternative analgesia has played a significant deciding role in labor analgesia. In our case, the patient chose not to have any attempts at neuraxial analgesia at all and preferred to have intravenous analgesia via PCA. At that time, she was already in severe pain from the contractions of advanced labor and requested immediate pain relief. Also, the attending anesthesiologist, taking into account the possibility of a failed epidural because of the patient's AS, decided in favor of the remifentanil PCA.

Intravenous remifentanil, has become an alternative for labor analgesia, the first published use in year 2000. Remifentanil is a selective mu-agonist similar in potency to fentanyl. It's pharmacokinetic profile of rapid onset (peak effect in 60-80 seconds) and rapid metabolism by nonspecific plasma and tissue esterase (context sensitive half time of 3 minutes) make it easily titratable, and it does not accumulate. This characteristic of remifentanil makes it beneficial for brief, cyclical periods of pain such as uterine contractions. Remifentanil's use in labor can be limited by both maternal and fetal effects. Just like the commonly used opioids such as fentanyl, pethidine, and sufentanil, hypoventilation and oxygen desaturation can occur in parturients receiving remifentanil. This has been shown in the early studies of its use, subjects observed to have brief periods of desaturation, relieved immediately by oxygen supplementation.[12] Although there is a high rate of placental transfer (remifentanil being highly lipophilic and the placenta being well perfused), studies have confirmed that remifentanil does not cause severe effects on the neonate, confirming remifentanil's rapid metabolism and redistribution in the neonate after placental transfer.[13]

The use of remifentanil PCA for labor analgesia varies among institutions. Some still consider it as "off-label use" while some have advocated its routine use.[14] It has been considered as first-line option or alternative if NA is contraindicated among their parturients.[15] Ronel et al.,[3] in their extensive literature review had these findings: Compared with epidural analgesia (bupivacaine, ropivacaine or levobupivacaine with an opioid: fentanyl or sufentanil), remifentanil PCA has shown inferior analgesia (early and late stages of labor), more maternal respiratory depression, but similar rates for outcomes (spontaneous, instrumental, or abdominal deliveries).

Several dose finding studies have been conducted in the past decade with varying results. Protocols vary in the bolus dose (0.1-1 μg/kg), lockout interval (1-5 minutes), and presence or absence of a background infusion. In our patient, remifentanil PCA was started in the first stage of labor consistent with recommendations in the literature. The initial settings were: bolus dose of 20 mcg (0.25 μg/kg) and a lockout period of 3 minutes. There was no background infusion. This was a reasonable initial setting comparable to most studies reviewed. A bolus of 20–40 μg (0.25–0.5 μg/kg) is used most widely. The bolus dose was increased to 40 μg (0.5 μg /kg) and the lockout interval decreased to 2 minutes in the latter part of active labor as the initial dose became inadequate to provide analgesia. This was consistent with findings of frequent adjustment in PCA settings as labor progressed. As shown by a recent study, there was a need to adjust both the bolus and the background infusion to a higher dose as the labor shifted from latent to active.[16] In our patient, the absence of background infusion remained until delivery. The decision to avoid incorporation of a background infusion of remifentanil in our patient's PCA settings from the start to finish was based on reports that it increases the incidence of severe adverse effects, especially in our patient who has concomitant COVID-19.[5] These settings could have been changed but for the patient, it was not necessary as she verbalized comfort even with a score of 5/10. This was important as the goal of labor analgesia was not total elimination of pain, but to decrease pain to the patient's comfortable level.

Throughout the labor process, the patient was vigilantly monitored for adverse effects of remifentanil such as excessive sedation, nausea, vomiting, pruritus, bradycardia, and desaturation by a dedicated team of obstetrician, anesthesiologist, nurses, and medical interns. Our patient, tested positive for SARS-CoV-2 infection, hence the use of opioids must be dealt with caution. Opioids in

general can depress the respiratory system and reduce ventilation by lowering the responsiveness of the medullary respiratory centers to hypoxia and hypercapnia. In a review of pharmacologic considerations among pregnant patients positive for COVID-19, remifentanil was mentioned as a good alternative for labor analgesia, with caution that opioid-induced vomiting can contribute to virus aerosolization.[17] Although our patient did not have respiratory symptoms related to COVID-19, supplemental oxygen was initiated. Close monitoring by a dedicated person ensured that the possible remifentanil-associated respiratory depression and patient desaturation were addressed promptly.

There was oxygen supplementation via a Hudson face mask upon admission and even before initiation of remifentanil PCA, as the patient was also at risk of respiratory distress from the COVID-19. This was in line with published literature on the ideal 1:1 nursing care and supplemental oxygen whenever remifentanil PCA was used. There was no recorded reduction in oxygen saturation seen via a pulse oximeter. Capnography to detect hypoventilation wasn't employed. She was fully awake and responsive to constant prodding and communication with the team. The patient delivered via spontaneous vaginal delivery after almost three hours of labor. The baby showed no signs of opioid depression with an APGAR score of 9 after 1 minute, and remaining 9 after 5 minutes. The patient reported satisfaction with her labor experience, including absence of adverse effects such as nausea, vomiting, pruritus, or drowsiness. Collated reports of remifentanil PCA use in labor in Switzerland, with information about maternal satisfaction and adverse effects, has shown that 82% of women reported that they were either satisfied or very satisfied with their labor analgesia[3] thus, emphasizing the importance of patient feedback.

CONCLUSION

Pregnancy complicated by AS and COVID-19 pose challenges to the anesthesiologist. Alternatives to neuraxial analgesia for labor should be sought when relative contraindications and patient preference point against it. This paper reports the successful management of labor analgesia by using remifentanil PCA.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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