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Use of Atropine, Ondansetron, and Ketorolac in Suspected Amniotic Fluid Embolism

Luis D. Pacheco, Shannon M. Clark, Karin Fox, Melissa E. Bauer, Steven L. Clark

Authors and Affiliations

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Abstract In Brief

Amniotic fluid embolism (AFE) is a rare, life-threatening obstetric event associated with extremely high maternal and perinatal morbidity and mortality with no known definitive pathophysiologic pathway. Current recommended management strategies are mainly supportive and include high-quality cardiopulmonary resuscitation and prompt delivery of the potentially viable fetus to improve neonatal survival and maternal resuscitation. More recently, case reports have described success in the resuscitation of patients with presumed AFE with a protocol that includes intravenous administration of atropine (1 mg), ondansetron (8 mg), and ketorolac (30 mg). The currently available evidence for the use of atropine, ondansetron, and ketorolac to treat AFE is limited, consisting of only case reports. As a result, the potential harms, including worsening of bleeding or coagulopathy, worsening kidney function, maternal tachycardia, cardiac arrhythmias, and myocardial injury, with the use of atropine, ondansetron, and ketorolac in cases of suspected AFE must be considered. We caution

against the widespread use of this protocol for suspected cases of AFE and remind clinicians of the many disappointing histories of medical interventions later discredited. We recommend that adequately oxygenating, supporting blood pressure, treating heart failure, and aggressively managing coagulopathy remain the mainstays of therapy and should be recognized as the standard of care.

Amniotic fluid embolism (AFE) is a rare, life-threatening obstetric event associated with extremely high maternal and perinatal morbidity and mortality.[1] Amniotic fluid embolism classically presents as a triad of cardiovascular collapse, respiratory failure, and coagulopathy during labor or within 30 minutes of placental delivery.[2,3] Although various hypothetical pathophysiologic pathways have been described (including fetal tissue passage to maternal circulation with mechanical obstruction of the pulmonary circulation and development of an “anaphylactoid reaction” mediated by different vasoactive substances), the cause of AFE remains largely unknown.[2] Therefore, current recommended management strategies are mainly supportive and include high-quality cardiopulmonary resuscitation, prompt delivery of the potentially viable fetus to improve neonatal survival and to augment efficacy of maternal resuscitation, early identification and hemodynamic management of right ventricular failure, medical and surgical control of bleeding (eg, uterine atony, pelvic lacerations), lung protective mechanical ventilation, and optimized postresuscitation critical care.[2]

In recent years, several case reports have described success in the resuscitation of patients with presumed AFE with a protocol that includes atropine, ondansetron, and ketorolac as an adjunct to standard resuscitation efforts. The protocol involves intravenous administration of atropine (1 mg), ondansetron (8 mg), and ketorolac (30 mg) after clinical suspicion of AFE. These case reports have been the basis for some practitioners to recommend including atropine, ondansetron, and ketorolac in emergency kits and crash carts in labor and delivery units to facilitate their rapid administration in cases of maternal collapse and cardiac arrest suspected to be associated with AFE.[4,5] Here, we review the available evidence and use of atropine, ondansetron, and ketorolac with the aim of maintaining patient safety through evidence-based medicine.

AVAILABLE EVIDENCE FOR THE USE OF ATROPINE, ONDANSETRON, AND KETOROLAC

At present, the only available evidence for the use of atropine, ondansetron, and ketorolac to treat AFE consists of case reports. Case reports are particularly prone to publication bias, and aspects of the published case reports raise serious concerns. Many of the existing reports describe the same proposed hypothetical mechanisms of action: a reduction in pulmonary vascular resistance and platelet activation through blockade of serotonin and thromboxane A2 with the use of ondansetron (a serotonin-5HT3-receptor blocker) and ketorolac (a nonselective cyclooxygenase inhibitor), respectively, combined with atropine (antimuscarinic agent) to block an "increase in vagal response associated with AFE."[6–9] The latter recommendation appears to be based primarily on prior animal models of pulmonary embolism and pulmonary hypertension using bone marrow and glass beads to induce pulmonary embolism and rat models studying the effect of statins in chronic obstructive pulmonary disease,[10–12] neither of which is specific to the unique pathophysiology of AFE and is not likely to translate directly into human responses because of interspecies differences.

Proponents of the atropine, ondansetron, and ketorolac protocol suggest that inhibiting thromboxane A2 with ketorolac "blocks" the cause of coagulopathy in AFE.[6] We are unaware of any supportive data or practice guidelines in medicine recommending thromboxane A2 or serotonin blockade to treat acute or chronic elevations of pulmonary arterial pressures resulting in right ventricular failure or recommending the use of nonsteroidal anti-inflammatory drugs (NSAIDs) to block or correct any coagulopathy.

The description of the proposed atropine, ondansetron, and ketorolac protocol varies within published studies, with different atropine doses recommended ranging from 1 mg (used in most case reports) to 0.2 mg.[5,7] The latter is particularly worrisome because atropine doses lower than 0.4 mg may result in paradoxical bradycardia or even asystole attributable to a promuscarinic effect.[13]

It is important to note that the description of the clinical course in many of the case reports raises serious doubts about not only whether the diagnosis of AFE was accurate but also the efficacy of the proposed intervention. For example, Berry et al[9] described a case of atypical AFE that resolved after implementation of atropine, ondansetron, and ketorolac. The patient was 45 minutes postpartum and developed fever, chills, tachycardia, hypertension, stridor, and respiratory distress requiring intubation and mechanical ventilation. After intubation, the patient received atropine, ondansetron,

and ketorolac with improvement in oxygenation. The onset of symptoms 45 minutes after delivery, together with the fact that fever, hypertension, and stridor are not typically associated with AFE, makes this case unlikely to be AFE but rather an infection or aspiration. There was no evidence of bleeding or abnormal coagulation laboratory tests, further decreasing the likelihood that this was an AFE.[9] Similarly, Rezai et al[6] reported an atypical AFE case treated with atropine, ondansetron, and ketorolac. After cesarean delivery under general anesthesia (propofol and succinylcholine used for induction) for fetal indications, the patient developed systemic hypotension and hypoxemia with an end-tidal carbon dioxide of 0 mm Hg (despite no cardiac arrest described in the case). Phenylephrine boluses were administered together with atropine, ondansetron, and ketorolac, and the patient improved after the interventions. Although uterine atony was described, there was no clinical or laboratory evidence of coagulopathy. The absence of coagulopathy and hemodynamic improvement with phenylephrine are more consistent with propofol-induced vasodilation and hemodynamic instability than with AFE.

Other reports of success with the use of atropine, ondansetron, and ketorolac were despite recurrent cardiac arrest for prolonged periods of time after the administration of the protocol. Long et al[8] reported a case consistent with the clinical presentation of AFE. However, after atropine, ondansetron, and ketorolac administration, the patient had two further episodes of pulseless electrical activity and required further doses of epinephrine, dobutamine, and alteplase over a 53-minute period before achieving a steady return of pulse.[8] The lack of response over 50 minutes makes it unlikely that the atropine, ondansetron, and ketorolac treatment was beneficial. Furthermore, in a recent case, the authors describe the use of atropine, ondansetron, and ketorolac for AFE even though atropine was not administered.[7] Other authors have described the lack of benefit of the protocol in suspected cases of AFE.[14]

Table 1 summarizes the findings of seven published case reports identified through a literature search of MEDLINE (PubMed), CINAHL, and Scopus performed in March 2025, using the terms “AOK,” “atropine,” “ondansetron,” “ketorolac,” and “amniotic fluid embolism,” with no limitations for publication date or language.

Case Report	Brief Summary	Comments
French et al, 2024[7]	Cervical ripening at 38 wk of gestation with misoprostol and a Foley balloon. Sudden onset of persistent fetal bradycardia requiring emergency cesarean delivery under general anesthesia (hypoxemia noted before intubation). ST-segment depression with hypotension requiring vasopressors. Diffuse surgical oozing prompted A-OK administration for suspected AFE. Bakri balloon, multiple transfusions, and interventional radiology embolization performed to abate bleeding.	Atropine dose cited as 0.2 mg (not consistent with the recommended dose of 1 mg) but was not administered because of maternal tachycardia. Thus, patient did not receive the A-OK protocol.
Long et al, 2022[8]	Cardiovascular collapse and respiratory failure 15 min after delivery by cesarean at 39 wk. Pulseless electrical activity documented, together with right ventricular failure and coagulopathy.	After A-OK administration, patient had recurrent episodes of pulseless electrical activity for 53 min, requiring additional doses of epinephrine, dobutamine, and alteplase.
Berry et al, 2022[9]	45 min after a term vaginal delivery, patient developed fever, tachycardia, hypertension, and stridor with hypoxemia requiring endotracheal intubation. No evidence of coagulopathy.	Case not suggestive of AFE. Article describes contradictory doses of atropine in the Discussion.
Wothe et al, 2022[4]	During induction at 39 wk, patient developed fetal bradycardia and collapsed, requiring an emergency cesarean delivery under general anesthesia. A-OK was administered at the time of intubation. Despite this treatment, the patient developed pulseless electrical activity and pulseless ventricular tachycardia requiring multiple defibrillations and prolonged chest compressions. Patient ultimately required VA-ECMO.	Time elapsed between A-OK administration and return of spontaneous circulation not consistent with immediate benefit of the intervention. Abstract describes A-OK as "adenosine, ondansetron, ketorolac" instead of atropine, ondansetron, and ketorolac.
Rezai et al, 2017[6]	Patient underwent emergency cesarean delivery under general anesthesia (200 mg propofol and 100 mg succinylcholine for induction) for nonreassuring fetal status in the setting of maternal fever, tachycardia, and mild tachypnea. After delivery, patient developed hypotension, hypoxemia, and an end-tidal CO_2 level of 0 mm Hg (no pulses lost). Patient received multiple phenylephrine boluses, fluids, and A-OK. No coagulopathy described.	Atypical clinical presentation. Atropine dose used was 0.2 mg (not consistent with the recommended dose of 1 mg).
Sundin et al, 2024[5]	Patient presented at 34 wk in labor with a fetus in breech presentation. Suspicion for placental abruption prompted delivery by cesarean with neuraxial anesthesia. After delivery, patient developed cardiac arrest and received A-OK. Despite this treatment, the patient remained in asystole and persisted in and out of cardiac arrest for at least 20 min. At that time, VA-ECMO was initiated.	Time elapsed between A-OK administration and return of spontaneous circulation not consistent with immediate benefit of the intervention. Atropine dose of 0.2 mg used (not consistent with the recommended dose of 1 mg).
Gitman et al, 2019[14]	Cesarean delivery at 34 wk because of preeclampsia with severe features and multiple uterine leiomyomas. After delivery, patient developed cardiac arrest requiring multiple rounds of epinephrine and chest compressions. Despite use of A-OK, patient remained in cardiac arrest requiring VA-ECMO.	Time elapsed between A-OK administration and return of spontaneous circulation not consistent with immediate benefit of the intervention.

A-OK, atropine, ondansetron, ketorolac; AFE, amniotic fluid embolism; VA-ECMO, venoarterial extra corporeal membrane oxygenation.

Table 1. Published Case Reports of the Atropine, Ondansetron, and Ketorolac Protocol for Suspected Amniotic Fluid Embolism Cases

POTENTIAL HARMS ASSOCIATED WITH ATROPINE, ONDANSETRON, AND KETOROLAC

The use of NSAIDs (eg, ketorolac) in the setting of AFE may result in worsening of bleeding or coagulopathy, kidney function, and myocardial injury. Ketorolac-induced thromboxane A2 inhibition leads to significant platelet dysfunction lasting up to 24 hours after intravenous administration, potentially augmenting AFE-related coagulopathy or bleeding from uterine atony.[15] Similarly, prostaglandin depletion secondary to NSAIDs results in renal afferent arteriolar vasoconstriction, decreasing glomerular perfusion and increasing the risk of acute kidney injury.[16] The latter is of particular concern during severe systemic hypotension and clotting cascade

activation, with disseminated intravascular coagulation resulting in severe multiorgan hypoperfusion, as seen with AFE. Finally, the detrimental effects of NSAIDs on myocardial recovery and healing after ischemic events, as may occur after cardiac arrest in AFE, have also been described.[17]

Atropine, an antimuscarinic agent indicated for the treatment of symptomatic bradycardia, was removed from advanced cardiovascular life support algorithms in 2010 because of the lack of benefit in the setting of cardiac arrest from nonshockable rhythms, including pulseless electrical activity and asystole (did not improve rate of return of spontaneous circulation, survival to hospital discharge, or survival with favorable neurologic outcomes).[18] Besides the lack of benefit in the setting of cardiac arrest, the use of atropine commonly results in significant tachycardia that may be detrimental for patients with acute right ventricular failure, as commonly seen in AFE.[1,2] Tachycardia shortens the diastolic filling time of the right ventricle, compromising its preload and cardiac output even further.

The use of the serotonin receptor antagonist ondansetron is associated with QT interval prolongation and an increased risk of cardiac arrythmias, including polymorphic ventricular tachycardia (eg, torsade de pointes).[19] Amniotic fluid embolism–related acute right atrial and ventricular dilation, acidosis from hypercarbia, elevated lactic acid levels, and systemic hypoxemia may increase the risk of life-threatening arrythmias in conjunction with ondansetron administration.

CONCLUSION

Amniotic fluid embolism is a complex event with an incompletely understood pathophysiology. Thus, best practice involves aggressive supportive treatment addressing the most life-threatening complications, including acute right ventricular failure, coagulopathy, and respiratory failure. This is the only recommended strategy at present. Until we have a better understanding of AFE, specific interventions targeting specific but entirely hypothetical pathophysiologic disease pathways are unlikely to be of benefit and may be harmful. At present, there is insufficient evidence supporting the benefits of atropine, ondansetron, and ketorolac therapy. Given current AFE survival statistics of 40–80%, reports of a few patients who may have had AFE treated with atropine, ondansetron, and ketorolac and did not die in association with, or despite treatment with, this unproven

and potential harmful therapy should not be considered evidence of efficacy.

We caution against the widespread use of the atropine, ondansetron, and ketorolac protocol for suspected cases of AFE and remind clinicians of the many disappointing histories of medical interventions later discredited after extensive robust basic science, translational, and clinical research. Ensuring adequate oxygenation, supporting blood pressure, treating heart failure, and aggressively managing coagulopathy remain the mainstays of therapy and should be recognized as the standard of care.

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