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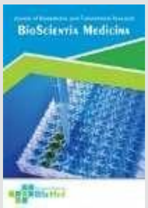

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Rare and Fatal Complication: A Case of Ketorolac-Induced Anaphylaxis Leading to Cardiac Arrest and Hypoxic-Ischemic Brain Injury in a Young Adult

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A B S T R A C T

Background: Anaphylaxis is a severe, life-threatening allergic reaction that can lead to cardiac arrest and hypoxic-ischemic brain injury (HIBI). Ketorolac, a nonsteroidal anti-inflammatory drug (NSAID) commonly used for postoperative pain management, has been rarely associated with anaphylaxis. **Case presentation:** We present the case of a 32-year-old woman who developed anaphylaxis and subsequent cardiac arrest following intravenous administration of ketorolac after an appendectomy. Despite successful resuscitation, the patient suffered from HIBI and remained in a persistent vegetative state. **Conclusion:** This report highlights the potential for fatal complications associated with ketorolac administration and emphasizes the importance of prompt recognition and management of anaphylaxis in the perioperative setting. This case underscores the need for heightened vigilance regarding potential anaphylactic reactions to ketorolac, even in patients with no prior history of drug allergies. Early recognition and aggressive management of anaphylaxis are crucial to minimize the risk of severe complications like cardiac arrest and HIBI.

1. Introduction

Anaphylaxis, a severe and potentially life-threatening allergic reaction, is characterized by its rapid onset and systemic manifestations. It is a complex clinical syndrome resulting from the sudden release of inflammatory mediators from mast cells and basophils, leading to widespread vasodilation, increased capillary permeability, and bronchoconstriction. These physiological changes can culminate in cardiovascular collapse, respiratory failure, and even death if not recognized and treated promptly. The incidence of anaphylaxis has been rising globally, with increasing recognition of its diverse triggers and clinical presentations. While the exact prevalence remains uncertain, recent estimates suggest that anaphylaxis affects approximately 0.5-2% of the population, with variations across different regions and age groups. The clinical manifestations of anaphylaxis are highly variable, ranging from mild cutaneous symptoms to life-threatening cardiovascular and respiratory compromise. Common symptoms include urticaria, angioedema, pruritus, flushing, dyspnea, wheezing, stridor, hypotension, and syncope. The severity of anaphylaxis can be unpredictable, and even individuals with a history of mild reactions can experience severe episodes. The rapid progression of symptoms underscores the importance of prompt recognition and intervention to prevent fatal outcomes.[1-3]

A wide range of triggers can elicit anaphylaxis, including medications, foods, insect stings, and latex. Among medications, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and biological agents are frequently implicated. Food-induced anaphylaxis is most commonly triggered by peanuts, tree nuts, shellfish, milk, and eggs. Insect stings, particularly from bees, wasps, and hornets, can also cause anaphylaxis in susceptible individuals. Latex allergy is a concern for healthcare workers and patients with multiple surgical procedures. The diagnosis of anaphylaxis is primarily clinical, and based on the recognition of characteristic signs and symptoms. The presence of skin manifestations, such as urticaria or angioedema, along with respiratory or cardiovascular compromise, strongly suggests anaphylaxis. However, the absence of skin findings does not exclude the diagnosis, as anaphylaxis can present with isolated respiratory or cardiovascular symptoms. In equivocal cases, laboratory tests, such as serum tryptase levels, can be helpful in confirming the diagnosis.[4-6]

The cornerstone of anaphylaxis management is the immediate administration of intramuscular epinephrine. Epinephrine is a potent vasoconstrictor and bronchodilator that counteracts the pathophysiological effects of anaphylaxis. It should be administered promptly upon recognition of symptoms, even in mild cases, as delays in treatment can increase the risk of severe complications. Additional supportive measures, such as oxygenation, intravenous fluids, and airway management, may be necessary depending on the severity of the reaction. Prevention of anaphylaxis involves identifying and avoiding triggers, educating patients and caregivers about the signs and symptoms of anaphylaxis, and ensuring access to self-injectable epinephrine for individuals at risk. For patients with a history of anaphylaxis, meticulous documentation of triggers and previous reactions is essential to guide future management.[7-10] In this case report, we present a rare and tragic case of ketorolac-induced anaphylaxis leading to cardiac arrest and hypoxic-ischemic brain injury (HIBI). Ketorolac, a nonsteroidal anti-inflammatory drug (NSAID) commonly used for postoperative pain management, has been rarely associated with anaphylaxis. The patient, a 32-year-old woman with no prior history of drug allergies, developed anaphylaxis and subsequent cardiac arrest following intravenous administration of ketorolac after an appendectomy. Despite successful resuscitation, the patient suffered from HIBI and remained in a persistent vegetative state.

2. Case Presentation

This report details the case of a 32-year-old female who presented to the hospital with acute appendicitis. She had no known allergies and a body mass index (BMI) of 27.8 kg/m². Pre-operative assessment revealed no significant medical history; Intra-operative Period: The patient underwent an uncomplicated laparoscopic appendectomy under spinal anesthesia. The procedure lasted approximately 45 minutes without any notable intraoperative complications; Immediate Post-operative Period (within minutes): Approximately 3 minutes after the completion of the surgery, the patient received 30 mg of intravenous ketorolac for post-operative pain management. Shortly after the administration of ketorolac, she exhibited signs of restlessness and facial flushing, followed by a rapid deterioration in her clinical status. The patient experienced a sudden drop in blood pressure (hypotension) and a loss of consciousness. This was immediately followed by cardiac arrest and respiratory arrest. The constellation of symptoms, including the temporal relationship with ketorolac administration, strongly suggested anaphylaxis as the underlying cause of the cardiac arrest; Post-operative Day 1: Cardiopulmonary resuscitation (CPR) was initiated promptly and continued for 50 minutes until the return of spontaneous circulation (ROSC) was achieved. The patient was intubated and mechanically ventilated to support her respiratory function. She was also started on vasopressor support with norepinephrine and dobutamine to maintain adequate blood pressure and cardiac output. Upon neurological assessment, the patient demonstrated a Glasgow

Coma Scale (GCS) score of E2M4Vtt, indicating severe neurological impairment. Her blood pressure stabilized at 110/70 mmHg with a heart rate of 115 beats per minute, and her oxygen saturation was maintained at 98% with mechanical ventilation. Despite the profound neurological compromise, the patient exhibited some responses to painful stimuli and retained intact cough and gag reflexes. Her pupils were reactive to light, and a Babinski reflex was present, suggesting upper motor neuron dysfunction. Given the prolonged cardiac arrest and the neurological findings, hypoxic-ischemic brain injury (HIBI) was suspected as a consequence of the anaphylactic event. The patient's overall clinical picture was consistent with post-cardiac arrest syndrome (PCAS); Post-operative Day 2 to Day 5: Over the next few days, the patient experienced recurrent generalized tonic-clonic seizures, occurring 2-3 times per day, each lasting approximately 2 minutes. These seizures likely reflected the extent of the brain injury and the ongoing neuronal instability; Post-operative Day 10: The patient developed acute kidney injury (AKI), classified as KDIGO stage 3, characterized by a significant elevation in serum urea (122 mg/dL) and creatinine (3.05 mg/dL), along with oliguria (urine output 0.3-0.4 mL/kg/hour). This AKI likely resulted from a combination of factors, including the initial hypotensive episode during anaphylaxis, the potential nephrotoxic effects of medications, and the overall critical illness; Post-operative Day 24: A tracheostomy was performed to facilitate long-term airway management and ventilator weaning; Post-operative Day 25: The process of weaning the patient from mechanical ventilation was initiated; Post-operative Day 26: The patient developed a fever (38.6°C) accompanied by sputum retention and fine crackles in both lungs on auscultation. Laboratory investigations revealed leukocytosis (white blood cell count 28,150/μL), suggesting an infectious process. A chest X-ray confirmed the presence of infiltrates in both lungs, consistent with ventilator-associated pneumonia (VAP); Post-operative Day 28: The patient's clinical condition further deteriorated, with a Sequential Organ Failure Assessment (SOFA) score of 3, indicating multiple organ dysfunction. This, in conjunction with the presence of VAP, led to the diagnosis of sepsis; Post-operative Day 30: The patient's renal function showed signs of improvement, with an increase in urine output to 1.0 mL/kg/hour and a decrease in serum urea (45 mg/dL) and creatinine (0.36 mg/dL); Post-operative Day 32: The patient's hemodynamic status stabilized, and the signs of infection resolved with appropriate antimicrobial therapy and supportive care. However, she remained in a persistent vegetative state, as evidenced by a Coma Recovery Scale-Revised (CRS-R) score of 4 and a Modified Rankin Scale (MRS) score of 5. These scores indicated a lack of meaningful interaction with the environment and complete dependence on others for all aspects of care; Post-operative Day 42: The patient was transferred to a high-dependency unit (HCU) for ongoing care and rehabilitation; Post-operative Day 52: The patient was discharged home with palliative care arrangements in place. This case tragically illustrates the cascade of events that can unfold following a severe anaphylactic reaction. The initial insult of anaphylaxis led to cardiac arrest, which in turn resulted in HIBI and a persistent vegetative state. The patient's subsequent course was complicated by AKI, VAP, and sepsis, further highlighting the challenges in managing critically ill patients with multi-organ dysfunction (Table 1).

Following the diagnosis of anaphylaxis and subsequent cardiac arrest, the patient received immediate and aggressive treatment to support her vital functions and manage the complications that arose; Post-operative Day 1: Cardiopulmonary resuscitation (CPR) was promptly initiated and continued until the return of spontaneous circulation (ROSC) was achieved after 50 minutes. To maintain adequate blood pressure and organ perfusion, the patient was started on vasopressor support with norepinephrine at a dose of 0.1 μg/kg body weight/minute and dobutamine at 5 μg/kg body weight/minute. She was intubated and placed on mechanical ventilation with the following settings: assist-control (AC) mode, tidal volume (TV) of 450 mL, respiratory rate (RR) of 12 breaths per minute, positive end-expiratory pressure (PEEP) of 5 cmH_2O, and an inspired oxygen fraction (FiO_2) of 100%. Given the severity of her condition, the patient was referred to Arifin Achmad Regional General Hospital Pekanbaru, a tertiary care center with specialized intensive care capabilities; Post-operative Day 2: The patient's ventilatory support was adjusted to synchronized intermittent mandatory ventilation (SIMV) mode with a TV of 450 mL, RR of 12 breaths per minute, pressure support (PS) of 12 cmH_2O, PEEP of 5 cmH_2O, and FiO_2 of 70%. This adjustment aimed to provide more balanced ventilatory support while gradually encouraging spontaneous breathing efforts. The doses of norepinephrine and dobutamine were titrated down to 0.05 μg/kg body weight/minute and 5 μg/kg body weight/minute, respectively, as her hemodynamic status improved. A detailed neurological examination revealed a GCS score of E2M4Vett, indicating severe neurological impairment. However, she exhibited some response to painful stimuli and had intact cough and gag reflexes, suggesting some preserved brainstem function. Her pupils were reactive to light, and a Babinski reflex was present; Post-operative Day 2 to Day 7: The patient experienced recurrent generalized tonic-clonic seizures, which were treated with intravenous phenytoin at a dose of 100 mg every 8 hours. Despite this treatment, the seizures persisted, indicating ongoing neuronal irritability and the severity of the brain injury; Post-operative Day 10: The patient developed AKI, classified as KDIGO stage 3, with elevated serum urea (122 mg/dL) and creatinine (3.05 mg/dL), and oliguria (urine output 0.3-0.4 mL/kg/hour). This AKI likely resulted from a combination of factors, including the initial hypotensive episode during anaphylaxis, potential nephrotoxic effects of medications, and the overall systemic inflammatory response. Management focused on fluid optimization, close monitoring of electrolytes and renal function, and supportive care; Post-operative Day 24: A tracheostomy was performed to facilitate long-term airway management and ventilator weaning. This procedure aimed to reduce airway resistance, improve secretion clearance, and enhance patient comfort; Post-operative Day 25: The process of weaning the patient from mechanical ventilation was initiated using a T-piece with 5 L/min oxygen flow. This gradual weaning approach aimed to assess her ability to breathe spontaneously and maintain adequate oxygenation; Post-operative Day 26: The patient developed VAP, confirmed by fever, sputum retention, fine crackles in both lungs on auscultation, leukocytosis (WBC 28,150/μL), and chest X-ray showing infiltrates. Cultures identified *Klebsiella pneumoniae* and *Acinetobacter baumannii* as the causative organisms. She was started on appropriate antibiotics to target these pathogens; Post-operative Day 28: The patient's clinical condition deteriorated further, with a SOFA score of 3, indicating multiple organ dysfunction. This, in conjunction with the presence of VAP, led to the diagnosis of sepsis. Management included continued antibiotics, fluid resuscitation, and supportive care to address the systemic inflammatory response and organ dysfunction; Post-operative Day 30: The patient's renal function showed signs of improvement, with an increase in urine output to 1.0 mL/kg/hour and a decrease in serum urea (45 mg/dL) and creatinine (0.36 mg/dL). This improvement likely reflected the effectiveness of supportive care and the resolution of the underlying sepsis; Post-operative Day 32: The patient's hemodynamic status stabilized, and the signs of infection resolved with appropriate treatment. However, she remained in a persistent vegetative state, as evidenced by a CRS-R score of 4 and an MRS score of 5. These scores indicated a lack of meaningful interaction with the environment and complete dependence on others for all aspects of care; Post-operative Day 42: The patient was transferred to a high-dependency unit (HCU) for ongoing care and rehabilitation. This transition aimed to provide a less intensive level of care while continuing to monitor her condition and provide supportive therapies; Post-operative Day 52: The patient was discharged home with palliative care arrangements in place. This decision was made in consultation with her family and healthcare team, recognizing the poor prognosis for neurological recovery and the need to prioritize comfort and quality of life. This detailed account of the patient's treatment and follow-up highlights the complexity and challenges in managing a case of anaphylaxis leading to cardiac arrest and HIBI. The multidisciplinary approach involved prompt resuscitation, critical care management, pharmacological interventions, and supportive therapies. Despite these efforts, the patient's neurological outcome remained poor, underscoring the devastating consequences of severe anaphylaxis and the importance of early recognition and intervention (Table 2).

Table 1. Timeline of the disease, including anamnesis, clinical findings, laboratory and imaging findings, and the diagnosis.

Timeline	Anamnesis	Clinical finding	Imaging	Diagnosis
Pre-operative	32-year-old female, BMI 27.8, no known allergies, presented with acute appendicitis.	-	Acute appendicitis	-
Intra-operative	Underwent uncomplicated appendectomy under spinal anesthesia. The procedure lasted 45 minutes.	-	-	-
Post-operative - Immediate	3 minutes post-op, received 30mg ketorolac IV for pain management.	Restlessness, facial flushing, hypotension, decreased consciousness, cardiac arrest, respiratory arrest.	Anaphylaxis, cardiac arrest, respiratory arrest	-
Post-operative - Day 1	CPR was performed for 50 minutes with ROSC achieved. The patient was intubated and started on norepinephrine and dobutamine.	GCS E2M4Vtt, BP 110/70 mmHg, HR 115 bpm, SpO_2 98%, on mechanical ventilation, responded to pain, intact cough and gag reflexes, pupils reactive to light, Babinski reflex present.	HIBI (suspected), PCAS	-
Post-operative - Day 2	-	Generalized tonic-clonic seizures (2-3 times per day, lasting 2 minutes each, continued for 5 days).	-	-
Post-operative - Day 10	-	AKI - KDIGO stage 3, serum urea 122 mg/dL, creatinine 3.05 mg/dL, urine output 0.3-0.4 mL/kg/hour.	-	AKI
Post-operative - Day 24	-	Tracheostomy performed.	-	-
Post-operative - Day 25	-	Weaning from mechanical ventilation was initiated.	-	-
Post-operative - Day 26	-	Fever (38.6°C), sputum retention, fine crackles in both lungs, leukocytosis (WBC 28,150/µL).	Chest X-ray: infiltrates in both lungs.	VAP
Post-operative - Day 28	-	SOFA score of 3.	Sepsis	
Post-operative - Day 30	-	AKI improved, urine output 1.0 mL/kg/hour, serum urea 45 mg/dL, creatinine 0.36 mg/dL.	-	-
Post-operative - Day 32	-	Hemodynamically stable, signs of infection resolved, persistent vegetative state (CPC 4, MRS 5).	-	-
Post-operative - Day 42	-	Transferred to HCU.	-	-
Post-operative - Day 52	-	Discharged home with palliative care.	-	-

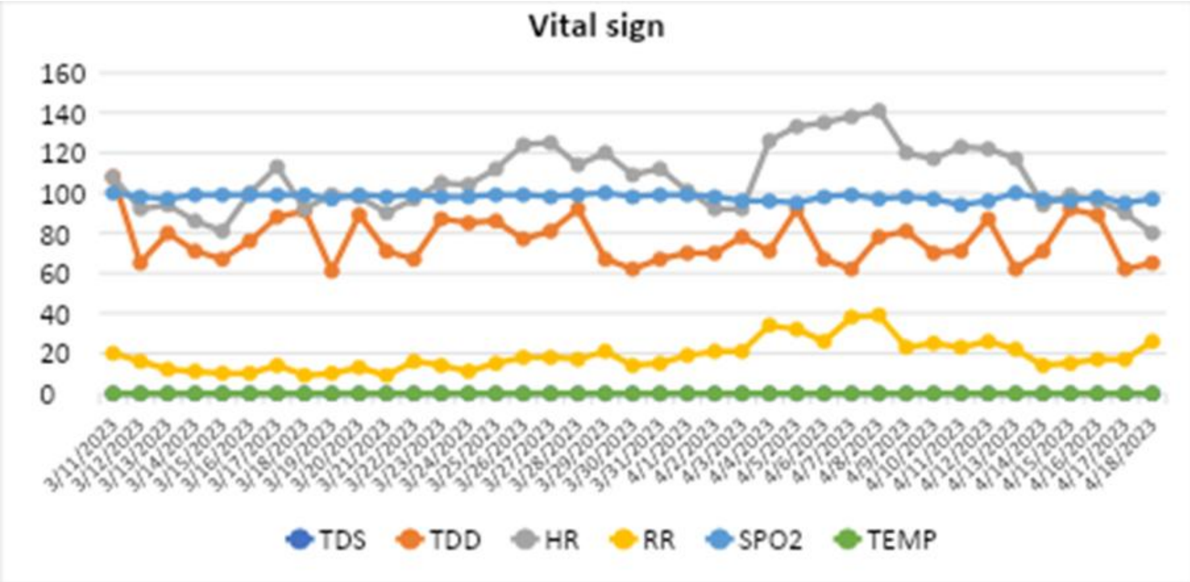

Figure 1. Patient vital signs during treatment.

Table 2. Treatment and follow-up.

Timeline	Treatment	Follow-up
Post-operative - Day 1	CPR, norepinephrine 0.1 μg/KgBB/minute, dobutamine 5 μg/KgBB/minute, mechanical ventilation (AC VC TV 450 RR 12 PEEP 5 FiO_2 100%).	Referred to Arifin Achmad Regional General Hospital Pekanbaru.
Post-operative - Day 2	Mechanical ventilation (SIMV VC TV 450 RR 12 PS 12 PEEP 5 FiO_2 70%), norepinephrine 0.05 μg/KgBB/min, dobutamine 5 μg/KgBB/min.	GCS E2M4Vett, BP 110/70 mmHg, HR 115 bpm, SpO_2 98%, responding to pain, intact cough and gag reflexes, pupils reactive to light, Babinski reflex present.
Post-operative - Day 2 to Day 7	Phenytoin 100 mg IV every 8 hours for seizures.	Continued seizures.
Post-operative - Day 10	-	AKI - KDIGO stage 3, serum urea 122 mg/dL, creatinine 3.05 mg/dL, urine output 0.3-0.4 mL/kg/hour.
Post-operative - Day 24	Tracheostomy.	-
Post-operative - Day 25	Weaning from mechanical ventilation was initiated with T-piece 5 L/min oxygen.	-
Post-operative - Day 26	Antibiotics for VAP (Klebsiella pneumoniae and Acinetobacter baumannii).	Fever, sputum retention, fine crackles in both lungs, leukocytosis (WBC 28,150/μL), chest X-ray showing infiltrates.
Post-operative - Day 28	-	Sepsis diagnosed (SOFA score 3).
Post-operative - Day 30	-	AKI improved, urine output 1.0 mL/kg/hour, serum urea 45 mg/dL, creatinine 0.36 mg/dL.
Post-operative - Day 32	-	Hemodynamically stable, signs of infection resolved, persistent vegetative state (CPC 4, MRS 5).
Post-operative - Day 42	-	Transferred to HCU.
Post-operative - Day 52	-	Discharged home with palliative care.

3. Discussion

Anaphylaxis is a severe and potentially life-threatening allergic reaction that demands immediate recognition and intervention. It is a systemic reaction, meaning it affects multiple organ systems throughout the body, and is characterized by its rapid onset, often occurring within seconds or minutes of exposure to a triggering allergen. This swift progression underscores the critical need for prompt action to prevent serious complications and potentially fatal outcomes. At the heart of anaphylaxis is the immune system's response to an allergen, a substance that is typically harmless but triggers an abnormal reaction in susceptible individuals. When an individual with a predisposition to anaphylaxis encounters an allergen, their immune system overreacts, leading to a cascade of events that culminate in the characteristic symptoms of this condition. Central to this immune response are mast cells and basophils, specialized cells found in tissues throughout the body. These cells contain granules filled with potent inflammatory mediators, such as histamine, leukotrienes, and prostaglandins. Upon encountering an allergen, these cells are activated and release their contents, setting off a chain reaction that affects various organ systems. Histamine, one of the key mediators released during anaphylaxis, acts on blood vessels, causing them to dilate and become leaky. This vasodilation leads to a sudden drop in blood pressure, a hallmark of anaphylaxis, which can result in dizziness, fainting, and even shock. The increased permeability of blood vessels allows fluid to leak into surrounding tissues, causing swelling, particularly in the face, lips, and tongue. Leukotrienes and prostaglandins, other potent inflammatory mediators, contribute to the respiratory symptoms often seen in anaphylaxis. They cause the muscles around the airways to constrict, leading to wheezing, shortness of breath, and difficulty breathing. In severe cases, this bronchoconstriction can progress to complete airway obstruction, posing a life-threatening situation. The gastrointestinal tract can also be affected during anaphylaxis, with symptoms such as nausea, vomiting, abdominal cramps, and diarrhea. These symptoms arise from the effects of inflammatory mediators on the smooth muscles and blood vessels in the digestive system. The skin is often the first organ to show signs of anaphylaxis, with the appearance of hives (urticaria), and red, itchy welts that can appear anywhere on the body. Angioedema, a deeper swelling of the skin and underlying tissues, may also occur, particularly around the eyes, lips, and tongue. The combined effects of these inflammatory mediators on multiple organ systems can lead to a life-threatening situation if not addressed promptly. The sudden drop in blood pressure can compromise blood flow to vital organs, including the brain and heart, leading to loss of consciousness, cardiac arrhythmias, and even cardiac arrest. The bronchoconstriction can impair oxygenation, leading to respiratory distress and potentially respiratory failure. The severity of anaphylaxis can vary widely, ranging from mild, localized reactions to severe, systemic reactions that can rapidly progress to life-threatening complications. Even individuals who have experienced mild reactions in the past can have a severe reaction upon subsequent exposure to the same allergen. This unpredictability underscores the importance of recognizing the signs and symptoms of anaphylaxis and seeking immediate medical attention, even if the initial symptoms seem mild. The diversity of potential triggers further complicates the picture. Medications, including antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and biological agents, are among the common culprits. Foods, such as peanuts, tree nuts, shellfish, milk, and eggs, are well-known triggers of anaphylaxis, particularly in children. Insect stings, especially from bees, wasps, and hornets, can also cause anaphylaxis in susceptible individuals. Latex allergy is a concern for healthcare workers and patients with multiple surgical procedures. Given the potential severity and rapid progression of anaphylaxis, early recognition and prompt intervention are paramount. The cornerstone of management is the immediate administration of epinephrine, a medication that counteracts the effects of the inflammatory mediators driving the reaction.

Epinephrine acts as a vasoconstrictor, raising blood pressure, and as a bronchodilator, opening up the airways. It should be administered intramuscularly, preferably in the thigh, as soon as the signs and symptoms of anaphylaxis are recognized. In addition to epinephrine, other supportive measures may be necessary, depending on the severity of the reaction. Oxygen therapy can help improve oxygenation, while intravenous fluids can help restore blood pressure and prevent shock. In severe cases, airway management, including intubation and mechanical ventilation, may be required to ensure adequate breathing. Prevention of anaphylaxis involves identifying and avoiding triggers, educating patients and caregivers about the signs and symptoms of anaphylaxis, and ensuring access to self-injectable epinephrine for individuals at risk. For patients with a history of anaphylaxis, meticulous documentation of triggers and previous reactions is essential to guide future management.[11,12]

Ketorolac tromethamine, a potent analgesic belonging to the nonsteroidal anti-inflammatory drug (NSAID) class, is widely utilized in clinical practice for the management of moderate to severe pain. Its efficacy in providing rapid and effective pain relief, coupled with its availability in various formulations, including intravenous (IV), intramuscular (IM), and oral, has made it a popular choice among clinicians, particularly in the perioperative setting. While generally regarded as safe and well-tolerated, ketorolac, like many other medications, carries the potential for adverse effects, including the rare but serious complication of anaphylaxis. Anaphylaxis, a severe and life-threatening allergic reaction, is characterized by a rapid onset of symptoms involving multiple organ systems, including the skin, respiratory system, cardiovascular system, and gastrointestinal tract. These reactions are triggered by the immune system's response to an allergen, a substance that is typically harmless but elicits an abnormal and exaggerated reaction in susceptible individuals. In the case of ketorolac, the exact mechanism by which it triggers anaphylaxis remains incompletely understood. However, current evidence suggests that it is likely mediated by an IgE-mediated hypersensitivity reaction, similar to other drug-induced anaphylaxis cases. This involves the activation of mast cells and basophils, immune cells that release a variety of inflammatory mediators, such as histamine, leukotrienes, and prostaglandins, upon encountering an allergen. These mediators cause widespread vasodilation, increased capillary permeability, and bronchoconstriction, leading to the characteristic symptoms of anaphylaxis, such as hypotension, wheezing, and urticaria. The incidence of ketorolac-induced anaphylaxis is considered to be very low, although the precise figures remain elusive due to underreporting and the challenges in establishing a definitive causal relationship between ketorolac administration and anaphylactic reactions. Nevertheless, the potential for ketorolac to trigger anaphylaxis, albeit rare, is well-documented in the medical literature, with numerous case reports and studies describing such incidents. The clinical manifestations of ketorolac-induced anaphylaxis are similar to those seen with other triggers, ranging from mild cutaneous symptoms to life-threatening cardiovascular and respiratory compromise. Common symptoms include urticaria, angioedema, pruritus, flushing, dyspnea, wheezing, stridor, hypotension, and syncope. The severity of anaphylaxis can be unpredictable, and even individuals with no prior history of drug allergies or previous mild reactions can experience severe and life-threatening episodes. The diagnosis of ketorolac-induced anaphylaxis is primarily clinical, based on the recognition of characteristic signs and symptoms following ketorolac administration. A thorough medical history, including any history of allergies or previous adverse drug reactions, is crucial in establishing the diagnosis. In equivocal cases, laboratory tests, such as serum tryptase levels, can be helpful in confirming the diagnosis, although they are not always readily available or conclusive. The management of ketorolac-induced anaphylaxis follows the same principles as the management of anaphylaxis triggered by other causes. The cornerstone of treatment is the immediate administration of intramuscular epinephrine, a potent vasoconstrictor and bronchodilator that counteracts the pathophysiological effects of anaphylaxis. Epinephrine should be administered promptly upon recognition of symptoms, even in mild cases, as delays in treatment can significantly increase the risk of severe complications and fatal outcomes. In addition to epinephrine, other supportive measures, such as oxygenation, intravenous fluids, and airway management, may be necessary depending on the severity of the reaction. In cases of cardiovascular collapse or respiratory failure, cardiopulmonary resuscitation (CPR) and advanced life support measures may be required. Prevention of ketorolac-induced anaphylaxis involves careful consideration of the risks and benefits of ketorolac administration, particularly in patients with a history of allergies or previous adverse drug reactions. Alternative analgesics should be considered in these patients, and if ketorolac is deemed necessary, it should be administered with caution and close monitoring. Patients should be educated about the potential for allergic reactions to ketorolac and advised to seek immediate medical attention if they experience any symptoms suggestive of anaphylaxis. Healthcare providers should maintain a high index of suspicion for ketorolac-induced anaphylaxis and be prepared to administer prompt and effective treatment.[13,14]

Anaphylaxis, a severe and potentially life-threatening allergic reaction, can trigger a cascade of events that may culminate in cardiac arrest and hypoxic-ischemic brain injury (HIBI), both of which carry devastating consequences. Cardiac arrest, characterized by the sudden cessation of effective blood circulation, is a dire complication of anaphylaxis, while HIBI, resulting from oxygen deprivation to the brain, can lead to irreversible neurological damage. Cardiac arrest in the context of anaphylaxis arises from the interplay of several pathophysiological mechanisms. The massive release of inflammatory mediators, such as histamine, leukotrienes, and prostaglandins, during anaphylaxis triggers widespread vasodilation, causing a precipitous drop in blood pressure. This hypotension, coupled with increased capillary permeability, which allows fluid to leak out of blood vessels and into surrounding tissues, reduces the effective circulating blood volume, compromising blood flow to vital organs, including the heart and brain. The heart, deprived of adequate blood supply, becomes increasingly vulnerable to rhythm disturbances and may ultimately cease to function effectively, leading to cardiac arrest. The lack of oxygen delivery to the brain during cardiac arrest sets the stage for HIBI, a condition that can have profound and often irreversible neurological consequences. HIBI is a type of brain injury that occurs when the brain is deprived of oxygen for a prolonged period, typically due to an interruption of blood flow. In the context of anaphylaxis, cardiac arrest is the primary cause of this oxygen deprivation, as the heart's inability to pump blood effectively halts the delivery of oxygen to the brain. The brain, a highly metabolically active organ, is exquisitely sensitive to oxygen deprivation. Even brief periods of oxygen deprivation can trigger a cascade of cellular events that lead to neuronal dysfunction and death. The initial insult of oxygen deprivation disrupts cellular energy production, leading to a depletion of adenosine triphosphate (ATP), the energy currency of cells. This energy depletion impairs the function of ion pumps, leading to an influx of calcium ions into neurons, triggering a series of damaging events, including the release of excitatory neurotransmitters, the generation of free radicals, and the activation of enzymes that degrade cellular components. The extent of brain injury in HIBI depends on the severity and duration of oxygen deprivation, as well as the individual's resilience and the presence of any pre-existing conditions that may increase vulnerability to brain injury. In mild cases, HIBI may result in temporary neurological deficits that resolve with time and rehabilitation. However, in severe cases, HIBI can lead to permanent brain damage, manifesting as a range of neurological impairments, including cognitive deficits, motor dysfunction, and even a persistent vegetative state, as observed in the case of our patient. The interplay of cardiac arrest and HIBI in anaphylaxis represents a critical challenge in the management of this severe allergic reaction. The prompt recognition and treatment of anaphylaxis are paramount to prevent the progression to cardiac arrest and minimize the duration of oxygen deprivation to the brain, thereby reducing the risk of HIBI. Epinephrine, the cornerstone of anaphylaxis management, plays a crucial role in counteracting the pathophysiological mechanisms that lead to cardiac arrest and HIBI. Its potent vasoconstrictor effects help restore blood pressure and improve blood flow to vital organs, while its bronchodilator effects help maintain airway patency and ensure adequate oxygenation. In cases where cardiac arrest has occurred, cardiopulmonary resuscitation (CPR) must be initiated immediately to restore blood circulation and oxygen delivery to the brain. The quality of CPR is critical in determining the outcome of cardiac arrest, as effective chest compressions and timely defibrillation, if necessary, can significantly improve the chances of survival and neurological recovery. Even after successful resuscitation from cardiac arrest, the journey towards recovery is often fraught with challenges, particularly in cases where HIBI has occurred. Post-cardiac arrest care focuses on mitigating the impact of HIBI and optimizing neurological recovery. This involves a multidisciplinary approach that includes critical care management, targeted temperature management, and neuroprotective strategies. Critical care management aims to stabilize the patient's physiological parameters, including blood pressure, oxygenation, and ventilation, and to address any complications that may arise, such as infections, organ dysfunction, and seizures. Targeted temperature management, which involves cooling the body to a slightly lower temperature, has been shown to improve neurological outcomes in patients with HIBI after cardiac arrest. Neuroprotective strategies, such as the administration of medications that reduce inflammation and oxidative stress, are also being investigated for their potential to mitigate brain injury and promote neurological recovery. The long-term impact of HIBI can be profound, affecting not only the individual but also their families and caregivers. Survivors of HIBI may experience a range of neurological deficits, including cognitive impairment, motor dysfunction, and communication difficulties. These deficits can significantly impact their ability to perform daily activities, maintain independence, and participate in social and vocational roles. The emotional and psychological impact of HIBI can also be substantial, with survivors and their families often facing challenges such as depression, anxiety, and post-traumatic stress disorder (PTSD). The burden of care for individuals with severe HIBI can be significant, requiring long-term rehabilitation and support services.[15,16]

Anaphylaxis, a severe and potentially life-threatening allergic reaction, demands immediate recognition and intervention to avert dire consequences, including irreversible organ damage and death. The cornerstone of anaphylaxis management rests on the timely administration of intramuscular epinephrine, a potent medication that counteracts the pathophysiological effects of this perilous condition. However, effective management extends beyond epinephrine, encompassing a range of supportive measures tailored to the severity of the reaction. The early recognition of anaphylaxis is paramount in preventing its progression to life-threatening complications. Healthcare providers, particularly those in the perioperative setting where medications and other potential allergens are frequently encountered, must maintain a high index of suspicion for anaphylaxis and be vigilant in identifying its characteristic signs and symptoms. Anaphylaxis typically manifests with a rapid onset of symptoms involving multiple organ systems, including the skin, respiratory system, cardiovascular system, and gastrointestinal tract. Skin manifestations, such as urticaria (hives) and angioedema (swelling), are often the earliest and most readily apparent signs. Respiratory symptoms, including wheezing, shortness of breath, and stridor (a high-pitched breathing sound), may indicate airway compromise. Cardiovascular symptoms, such as hypotension (low blood pressure), tachycardia (rapid heart rate), and syncope (fainting), signal circulatory collapse. Gastrointestinal symptoms, including nausea, vomiting, abdominal cramps, and diarrhea, may also occur. The presence of two or more of these symptoms following exposure to a potential allergen should raise a strong suspicion of anaphylaxis, prompting immediate action. It is crucial to remember that the severity of anaphylaxis can vary widely, and even individuals with a history of mild reactions can experience severe and life-threatening episodes. Therefore, any suspicion of anaphylaxis warrants prompt and aggressive intervention. Epinephrine, a potent catecholamine with both vasoconstrictor and bronchodilator properties, is the mainstay of anaphylaxis treatment. Its vasoconstrictor effects counteract the vasodilation and increased capillary permeability that contribute to hypotension and circulatory collapse. Its bronchodilator effects relieve bronchoconstriction, improving airway patency and oxygenation. Intramuscular administration of epinephrine is the preferred route, as it ensures rapid absorption and onset of action. The recommended injection site is the anterolateral aspect of the thigh (vastus lateralis muscle). The dose of epinephrine is typically 0.01 mg/kg body weight, up to a maximum of 0.5 mg for adults. In severe cases or when there is no response to the initial dose, epinephrine can be repeated every 5-15 minutes as needed. The timely administration of epinephrine is critical in preventing the progression of anaphylaxis to life-threatening complications. Delays in treatment can significantly increase the risk of severe outcomes, including cardiac arrest, respiratory failure, and death. Therefore, epinephrine should be administered promptly upon recognition of anaphylaxis, even in mild cases. In addition to epinephrine, a range of supportive measures may be necessary to manage anaphylaxis effectively. The specific interventions employed will depend on the severity of the reaction and the individual's clinical presentation. Oxygen therapy is often administered to improve oxygenation, particularly in individuals with respiratory distress. Intravenous fluids are used to restore blood pressure and prevent circulatory collapse. Airway management, including intubation and mechanical ventilation, may be required in severe cases with airway compromise or respiratory failure. Antihistamines, such as diphenhydramine (Benadryl) and H2 blockers, such as ranitidine (Zantac), can help alleviate the symptoms of anaphylaxis, but they are not a substitute for epinephrine. Corticosteroids, such as methylprednisolone (Solu-Medrol), may be administered to reduce inflammation and prevent late-phase reactions, but their onset of action is delayed, and they are not effective in the acute management of anaphylaxis. In cases of cardiac arrest, cardiopulmonary resuscitation (CPR) must be initiated immediately to restore blood circulation and oxygen delivery to vital organs. Early defibrillation, if indicated, can also be life-saving. Following the acute management of anaphylaxis, close monitoring is essential to ensure the resolution of symptoms and prevent recurrence. Patients should be observed for at least 4-6 hours after the initial reaction, as late-phase reactions can occur. Patients should also be educated about the potential triggers of their anaphylaxis and provided with strategies to avoid future exposure. They should be prescribed self-injectable epinephrine and trained on how to use it in case of a future reaction. Regular follow-up with an allergist is recommended to assess the need for further evaluation, such as allergy testing, and to develop a personalized anaphylaxis management plan.[17,18]

Anaphylaxis, a severe and potentially life-threatening allergic reaction, poses a significant health risk to individuals of all ages and backgrounds. While the unpredictable nature of anaphylaxis makes it impossible to completely eliminate the risk, a multi-pronged approach to prevention can substantially reduce the incidence and severity of these reactions. This approach involves a shared responsibility among healthcare providers, patients, families, and the community at large. A comprehensive medical history is the cornerstone of anaphylaxis prevention. It provides crucial insights into an individual's allergy history, previous adverse reactions to medications, and other risk factors that may predispose them to anaphylaxis. Healthcare providers should meticulously inquire about any known allergies, including allergies to medications, foods, insect stings, and latex. The severity and nature of previous allergic reactions should be documented, as even a history of mild reactions can indicate a potential for future severe reactions. Particular attention should be paid to patients with a history of asthma, eczema, or other allergic conditions, as these individuals may be at increased risk for anaphylaxis. Additionally, patients with a family history of anaphylaxis or mast cell disorders should be considered high-risk. In the perioperative setting, where medications and other potential allergens are frequently encountered, a thorough medical history is especially critical. Patients should be questioned about any previous adverse reactions to anesthesia or medications administered during or after surgery. The information gathered during the medical history should be carefully documented and readily accessible to all healthcare providers involved in the patient's care. This shared knowledge can help identify potential triggers and guide decisions regarding medication choices, diagnostic testing, and preventive strategies. Empowering patients and their families with knowledge about anaphylaxis is essential in preventing and managing these reactions. Education should focus on the signs and symptoms of anaphylaxis, potential triggers, and the importance of seeking immediate medical attention if a reaction occurs. Patients should be taught to recognize the early signs of anaphylaxis, such as skin manifestations (urticaria, angioedema), respiratory symptoms (wheezing, shortness of breath), and cardiovascular symptoms (hypotension, tachycardia). They should be instructed to seek immediate medical attention if any of these symptoms appear following exposure to a potential allergen. Education about potential triggers is also crucial. Patients should be aware of the common triggers of anaphylaxis, including medications, foods, insect stings, and latex. They should be advised on strategies to avoid these triggers, such as reading food labels carefully, wearing medical alert bracelets, and informing healthcare providers about their allergies. Patients and their families should also be educated about the importance of having an anaphylaxis management plan. This plan should include instructions on how to administer self-injectable epinephrine, when to seek emergency medical care, and other preventive measures. Epinephrine, a potent medication that counteracts the effects of anaphylaxis, is a life-saving intervention for individuals at risk of these reactions. Patients with a history of anaphylaxis or a high risk of developing anaphylaxis should be prescribed self-injectable epinephrine and trained on how to use it. Self-injectable epinephrine is available in two main forms, auto-injectors and prefilled syringes. Auto-injectors, such as EpiPen and Auvi-Q, are designed for easy administration, even in emergency situations. They contain a pre-measured dose of epinephrine that is automatically injected into the thigh muscle when the device is activated. Prefilled syringes, such as Symjepi, require manual injection but may be preferred by some patients or healthcare providers. Patients and their families should be trained on how to use the prescribed epinephrine device. They should be instructed on the proper injection technique, the importance of seeking immediate medical attention after using epinephrine, and the signs and symptoms that may indicate the need for a second dose. Healthcare providers should ensure that patients have access to epinephrine at all times, including when they are at school, work, or traveling. They should also encourage patients to carry an anaphylaxis management plan and medical alert identification. The perioperative setting, where medications and other potential allergens are frequently encountered, presents a unique challenge for anaphylaxis prevention. Healthcare providers must maintain a heightened awareness of the potential for anaphylaxis and take proactive steps to minimize the risk. A thorough preoperative assessment, including a detailed medical history and allergy screening, is essential. Patients with a history of allergies or previous adverse reactions to medications should be monitored closely during and after surgery. Medications that have been associated with a high risk of anaphylaxis, such as antibiotics, NSAIDs, and neuromuscular blocking agents, should be used with caution. Alternative medications should be considered whenever possible, and if high-risk medications are deemed necessary, they should be administered in a controlled environment with appropriate monitoring and resuscitation equipment readily available. Healthcare providers should be trained to recognize the signs and symptoms of anaphylaxis and be prepared to administer prompt and effective treatment. Epinephrine should be readily available in all perioperative areas, and all staff should be familiar with its use. Anaphylaxis prevention extends beyond the healthcare setting, involving the active participation of schools, workplaces, and the community at large. Schools should have anaphylaxis management policies in place, including procedures for identifying and managing students at risk. Staff should be trained to recognize the signs and symptoms of anaphylaxis and administer epinephrine. Workplaces should also have anaphylaxis management protocols, including procedures for identifying and managing employees at risk. First aid kits should be equipped with epinephrine auto-injectors, and designated personnel should be trained to administer them. Community education campaigns can raise awareness about anaphylaxis, its triggers, and prevention strategies. Public access to epinephrine, such as in restaurants and public spaces, can also help improve the response to anaphylactic emergencies.[19,20]

4. Conclusion

This case report presents a rare but serious complication of ketorolac administration, highlighting the potential for fatal outcomes associated with this commonly used analgesic. The patient's anaphylactic reaction, leading to cardiac arrest and hypoxic-ischemic brain injury, emphasizes the critical importance of early recognition and prompt management of anaphylaxis in the perioperative setting. Despite the rarity of ketorolac-induced anaphylaxis, this case underscores the need for heightened vigilance, even in patients with no prior history of drug allergies. Thorough medical history, patient education, and access to epinephrine are crucial components of anaphylaxis prevention. In the perioperative setting, healthcare providers must maintain a high index of suspicion for anaphylaxis and be prepared to administer prompt and effective treatment. This case serves as a poignant reminder of the shared responsibility in preventing and managing anaphylaxis. By raising awareness, promoting education, and advocating for preparedness, we can strive to minimize the risk of these potentially devastating reactions.

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