

Pediatric Deaths and Venipuncture

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Venipuncture is a routine and relatively safe and painless medical procedure, necessary for accurate diagnosis and treatment. However, given that pain related to medical procedures may have adverse effects for children, could venipuncture cause deaths in infants and children? We analyzed our cases of unexpected death after venipuncture and conducted a literature review on them. A vasovagal response to noxious stimuli may explain such a sudden death immediately after venipuncture, commonly presented as needle phobia, breath-holding spell, and reflex anoxic seizure in the literature, despite the fact that the current medical evidence is not enough to prove their casual relationship. In addition, pain prevention and management during medical procedure is incorporated in clinical guidelines for pediatric patients, because painful medical procedures negatively affect child development. Thus, prevention and management of pain related to medical procedure may be helpful to avoid an adverse vasovagal response to noxious stimuli from occurring.

Key Words: Phlebotomy; Sudden death; Phobia; Infant death; Autopsy; Forensic pathology

Introduction

Venipuncture has been commonly used for centuries as an invasive procedure in health care and it is very important in clinical management and prevention [1]. Despite some adverse effects occurring following venipuncture such as bruising at the site of puncture (tissue damage and even fainting), it is considered as a routine and relatively painless medical procedure if it is practiced in accordance with the guideline. However new evidence revealed that venipuncture may cause a long-term deleterious effects in children [2]. We experienced cases of sudden unexpected death of infants and children after venipuncture. And, they need

to be reviewed in hindsight for prevention of premature death. Therefore, we reviewed and analyzed our cases and conducted a literature review on them.

Materials and Methods

In order to search cases of sudden death after venipuncture, the death circumstances of all pediatric deaths consulted by our institute because of their medicolegal issues surrounding their sudden deaths from 2006 to 2016, were reviewed. Seven cases where sudden death occurred after venipuncture could be retrieved.

The death circumstances noted in medical records

were reviewed and analyzed, focusing on the acute event after venipuncture. Additionally, the past history or medical history of the deceased were reviewed, and the findings of postmortem examination and ancillary testing were also analyzed.

Results

The characteristic features in all seven cases, which were analyzed according to the death circumstances, postmortem examination, and ancillary testing are illustrated and summarized in Table 1.

1. Death circumstances

In case 1, a 48-day-old girl was admitted to a hospital due to fever. On that day, cardiac arrest suddenly occurred. She had no specific medical history. She had high fever (38.6°C) a day prior to admission. After admission, the medical staff tried to establish an intravenous line but failed. After several attempts, they were able to establish an intravenous line on her right arm. Suddenly, she developed cyanosis and then cardiac arrest and respiratory failure occurred. Cardiopulmonary resuscitation (CPR) was performed. She was admitted to the intensive care unit, but died the next day.

In case 2, a 34-day-old girl was admitted to a hospital due to fever. On the fifth hospital day, she died unexpectedly. She was born at 36 weeks' gestation and weighed 2.5 kg. She had no significant medical history after birth. She had high fever (38°C) the day before

admission. Upon admission, she had the following vital signs: heart rate, 160/min; respiratory rate, 48/min; and temperature, 38.1°C. She was administered antipyretics and antibiotics, following which her condition improved. Her intravenous catheter was removed on the fifth hospital day when her intravenous line was removed. After she was breast-fed for an hour, the medical staff reattempted to establish an intravenous line on her right arm. While the staff were inserting a needle for the intravenous line, she was found cyanotic and unconscious. A CPR was immediately performed. During intubation, a lot of milky secretions was noted. She eventually died after an hour of CPR.

In case 3, a 70-day-old boy was admitted to a hospital due to fever. On the day of admission, he died unexpectedly. He had no significant history. His guardian recalled that he had a fever 6 hours prior to admission. Upon admission, his vitals were as follows: body temperature, 37.4°C; heart rate, 168/min; and respiratory rate, 34/min. After physical examination, a possibility of sepsis was considered. Medical staff performed a venipuncture for blood tests, but they couldn't collect enough blood samples. So, they reattempted on the left and right arms to establish an intravenous access. Then, the staff noticed that the patient's lip turned cyanotic. At that time, her heart rate decreased to less than 100/min, and the oxygen saturation reduced to less than 60%. CPR was performed but he died after 6 hours.

In case 4, 18-month-old boy was admitted to a hospital for fever and whizzing. Unfortunately, he died unexpectedly on the day of admission. He had no

Table 1. Comparison of our cases of sudden death after venipuncture

Case No.	Sex	Age	Clinical symptom	Postmortem findings/Clinical history	Medical procedure	Cause of death
1	F	48D	Fever	Pneumonia	Venipuncture	Sepsis
2	F	34D	Fever	Diffuse alveolar damage, preterm baby	Venipuncture	Foreign body aspiration
3	M	70D	Fever	Horseshoe kidney, elevated tryptase (103.5 µg/L)	Venipuncture	Undetermined
4	M	18M	Fever, whizzing	Pneumonia, diffuse alveolar damage	Venipuncture	Pneumonia
5	M	8M	Cough, running nose, sputum	Acute bronchiolitis, multiorgan failure	Venipuncture	Acute bronchiolitis, breath holding spell
6	M	3D	Fever	Amniotic/meconium aspiration, elevated CRP (11.84 mg/dL), air embolism	Venipuncture	Undetermined
7	M	2M	Fever	Aspiration pneumonitis, mild dilatation of pelvis in left kidney	Venipuncture	Undetermined

D, day; M, month; CRP, C-reactive protein.

specific history. He had fever on day prior to admission. Upon admission, a blood test revealed acidemia (pH 7.166); so nasal oxygen was administered. And, fluid replacement was administered through intravenous route. After some time, he started screaming while the medical staff attempted to obtain another blood sample. So, the medical staff with the help of his mother placed him in the prone position and held his shoulders, back, and legs. While the staff was reattempting a venipuncture on his right arm, they noticed that he was no longer breathing. CPR was immediately performed. He was transferred to another hospital to receive further treatment but he eventually died.

In case 5, an 8-month-old boy was admitted to a hospital due to cough, running nose with a lot of sputum. He died unexpectedly on the day of admission. Wheezing was noted on physical examination. For further examination, the medical staff attempted to obtain some blood samples from the dorsum of his right feet, but failed. They tried another venipuncture on the left malleolus, and they were able to obtain a blood sample, at which point he started screaming and kicked the tube. They had to take another blood samples and re-inserted a needle for an intravenous line on his right ankle again. While they were applying a bandage on the venipuncture site, he stopped screaming and breathing and cyanosis was noted. CPR was performed and his spontaneous circulation returned. He suffered from acute bronchiolitis, pulmonary edema, pneumonia, hypernatremia, disseminated intravascular coagulopathy, sepsis, convulsion, hypoxic brain damage, and heart failure. He eventually died about 22 days after admission, despite intensive treatment.

In case 6, a male neonate born full term (40+5 weeks) was admitted to a hospital due to fever (37.6°C). Unfortunately, he died unexpectedly. He was born through vaginal delivery, with Apgar score of 9 after 1 minute and 10 after 5 minutes. Further evaluations were performed to determine the cause of his fever. A blood test revealed a C-reactive protein level of 11.84 mg/L. Medical staff noted signs of convulsion and cyanosis upon insertion of a needle on his hand. CPR was performed but he eventually died.

In case 7, a 2-month-old boy was admitted to a hospital due to fever. He died unexpectedly after 3

days of admission. He had no specific medical history. His chest radiography was unremarkable. Abdominal computed tomography (CT) revealed that his left kidney was mildly dilated. Urinary tract infection was considered as the cause of the fever based on the result of the urine analysis (white blood cell >100). Cefotaxime was administered for treatment. A blood test revealed low hemoglobin levels (8.4 g/dL), which indicate physiologic anemia, but his iron level was unremarkable. On the fourth day of hospitalization, his intravenous line was changed, and a venipuncture was performed to obtain a blood sample. During the procedure, he was found unresponsive and cyanosis was noted. He had no specific medical history.

2. Postmortem examination with ancillary testing

In case 1, her height was 61 cm, her crown-rump length was 43 cm, and her head circumference was 38 cm. A map-like erythema was observed on the forehead. A contusion due to CPR was observed on the sternal area. Several venipuncture marks were identified on the left inguinal area, right antecubital fossa, anteriolateral aspect of the right wrist, and dorsum of the both hands. On internal examination, macroscopically a focal hemorrhage was noted on the endocardium of the outflow tract of the left ventricle. And, there was no other significant findings. Microscopically, regional infiltration to alveolar walls by neutrophils and macrophages, congestion, and intraalveolar hemorrhages were found on the lung. The area of the map-like erythema on the forehead revealed congestion microscopically. Otherwise unremarkable. Lidocaine was detected on the toxicological tests, suggesting that it would be related to treatment. Sepsis was determined as the cause of death.

In case 2, her weight was 51.5 cm, weight was 4.2 kg, crown-rump length was 35 cm, and head circumference was 35.8 cm. She had venipuncture marks on the anterior aspect of the right wrist, both inguinal areas, and the anterior aspects of the both ankles. On the internal examination, there was no significant findings. Microscopically, thickened alveolar septa with regional fibrosis, lymphocytic infiltration, and regional formation of glassy membrane were observed on the lungs,

suggesting alveolar damage. Semisolid material-like coagulated milk was observed in the stomach and duodenum. There was no evidence of recent trauma. Acetaminophen and ampicillin was detected on toxicological tests, suggesting that they were related to her treatment. On microbiological tests by DNA analysis, *Acinetobacter baumannii* was identified on the pleural fluid, and *Acinetobacter baumannii* and *Klebsiella pneumoniae rhinoscleromatis* were identified on the pericardial fluid. The cause of death was determined as foreign body aspiration.

In case 3, his height was 60 cm, weight was 7.5 kg, crown-rump length was 44 cm, and head circumference was 41 cm. A contusion with abrasion due to CPR was observed on the sternal area. More than 20 marks of venipunctures were noted on the right and left lateral aspect of the neck, both wrists, dorsum of both hands, both inguinal areas, both ankles, and dorsum of both feet. On internal examination, there were no significant findings except a small amount of blood on the bronchial tree and a horse-shoe kidney. There were no evidence of recent trauma. Toxicological test was negative. A mast cell tryptase concentration of 103.5 µg/L was revealed on biochemical test. The cause of death remained unascertained.

In case 4, he was 86 cm in height, 10.2 kg in weight. Marks of venipunctures were observed on the right antecubital fossa, right lower arm, right wrist, dorsum of the right hand, both the right and left inguinal areas, and the dorsum of the right feet. On internal examination, inflammatory micronodules on the larynx and the pulmonary consolidation were noted. On microscopic examination, there were focal necrotizing inflammation on the larynx, and acute suppurative pneumonia with diffuse alveolar damage on the lungs, and reactive hyperplasia with focal nonspecific suppurative inflammation on the lymph nodes. A cytopathic change was noted on the submandibular salivary gland, suggesting viral infection. There were no evidence of recent trauma. The toxicological test revealed methylephedrine and chlorpheniramine, suggesting that they were related to treatment. The postmortem biochemical test was unremarkable. The cause of death was determined as pneumonia.

In case 5, he was 69 cm in height, 9.9 kg in weight.

Several venipuncture marks were observed on the left ankle and dorsum of the left feet. Early signs of bed sore were noted on some areas of the body. Sutured incision wounds which would be for chest tubes were observed on both flanks. On internal examination, necrosis and hemorrhage were noted on the free wall of the left ventricle, the right ventricle was dilated. An atrial septal defect (ostium secundum defect, 0.5 cm in diameter) was noted. Edema, congestion, and consolidation were noted on the lungs. Microscopically, acute bronchiolitis, focal acute suppurative pneumonia and organizing pneumonia, squamous metaplasia on the bronchial epithelium, regional diffuse alveolar damage, and a lot of macrophages in alveoli were noted on the lungs. Acute and subacute ischemic necrosis, calcification and hemorrhage was observed on the heart. Acute stress involution including macrophages infiltration, ambiguous distinction between cortex and medulla, loss of lymphoid tissue, and increased interlobular fibrous deposition was noted on the thymus. Necrotizing inflammation and squamous metaplasia was observed on the bronchial epithelia. Parenchymal necrosis, lymphocytic infiltration with macrophages, and gliosis were noted on the brain, and edema and congestion were identified on the brain stem. The toxicological test was negative. The cause of death was determined as acute bronchiolitis or/and breath holding spell.

In case 6, his height was 55 cm, weight was 3.6 kg, crown-rump length was 36 cm, head circumference was 34 cm, chest circumference was 33 cm, abdomen circumference was 31 cm, and foot length was 8 cm. Marks of venipuncture were identified on the dorsum of the left hand. On internal examination, subgaleal hemorrhage was noted. There was no evidence of recent trauma. Upon microscopic examination, squamous cells with eosinophilic granular materials and inflammatory cell infiltration were noted. The postmortem CT revealed extensive subcutaneous emphysema on the right arm and air density in the major vessels connected to the heart and in some cerebral vasculature. The postmortem toxicological test was negative, and the postmortem biochemical test was unremarkable. The cause of death was remained unascertained.

In case 7, his height was 58 cm, weight was 6.5 kg, crown-rump length was 43 cm, head circumference

was 41 cm, chest circumference was 42.5 cm, abdomen circumference was 42 cm, and foot length was 10 cm. Marks of venipuncture were identified on the right neck, left antecubital fossa, dorsum of the right hand, both inguinal areas, both ankle, and dorsum of both feet. Umbilical hernia was noted. On internal examination, diffuse alveolar damage with a few eosinophilic amorphous materials in alveolar space was noted on the right lung, which is suggestive of aspiration pneumonitis. Mild microvesicular fatty change was noted on the liver. The postmortem toxicological test was negative, and the postmortem biochemical test was unremarkable. The cause of death remained unascertained.

Discussion

The infants and children in our study died unexpectedly after venipuncturs. These circumstances of death do not fit the San Diego definition of sudden infant death syndrome, because their episodes were not related to sleep or unsafe sleep environment. They were admitted to a hospital due to fever or due to symptoms of respiratory infection, and pathological conditions such as pneumonia or bronchiolitis were also confirmed on the postmortem examination. Venipuncture was mandatory in our cases because those inflammatory or infectious diseases require further evaluations for accurate diagnosis and appropriate treatment. However, sepsis was unlikely in our cases because there were no signs of organ dysfunction or failure, and their clinical presentations were not as severe as those of sepsis or systemic inflammatory response syndrome. Mechanical asphyxia was also unlikely in most cases because the medical staff or the medical staff with help of their parents were holding their arms or legs during the procedure of venipuncture, without pressing the body. Moreover, cardiac arrest or cyanosis occurred a little later after completing venipuncture, not during the venipuncture. Regarding the 18-month-old boy in case 4, the medical staff and his parents forced him to a prone position and held of his shoulders, back or legs while performing the venipuncture, according to their statements, suggesting that a possibility of asphyxia cannot be excluded. However, detailed information

on the overall circumstance of death and time period between venipuncture and his death were not provided.

Regarding the cause of death, three of seven cases remained unascertained, and two cases were determined as pneumonia and acute bronchiolitis, one case as sepsis, and the remaining case as foreign body aspiration. Despite the fact that the cause of death was determined in four cases, these causes were only considered as a possible cause of death, because the pathologic findings which were identified at postmortem examination, reflected the pathologic condition around the time of death, not the time when the acute event occurred. In addition, the event occurred at the beginning of the clinical course or when the clinical course was improving. It implies that the deceased infants and children had symptoms and signs of diseases in accordance with the pathologic conditions, which were not enough to be a cause of death but were still pathologic findings on the postmortem examination. It seems to make a difference among our cases in ruling a cause of death despite the fact that their clinical presentations and circumstances of death were similar.

There have been some medical conditions that there may be an association between a needle procedure and its adverse psychological outcome. Needle phobia is recognized as part of a group of specific phobias of blood-injection-injury type in DSM-IV, classified as a subtype of phobia with familial links often showing extreme vasovagal response [3,4]. It is defined as fear and avoidance behavior against exposure to needles, which may be combined with physiological changes in cardiac electrical activity as an extreme vasovagal response to a stimulus [3]. Breath-holding spells (BHS) are defined as cyanotic or pallid spells complicated by the loss of consciousness, posturing, and generalized seizures [5]. Cardiac arrest or sudden death was reported followed by BHS, and there was a suggestion that BHS has an association with a seizure disorder or neurodevelopmental abnormalities. It is also called reflex anoxic seizures (RAS) because it presents seizure-like motions (stiffening and jerks) followed by cardiac arrest as a reflex response to a noxious or unpleasant stimulus [6]. All those three medical conditions have similar clinical presentations, and they have a common

pathophysiology, explained as vasovagal response to noxious or unpleasant stimuli, and sudden unexpected deaths were reported in all of those conditions just as our cases presented, although most of them have a favorable outcome.

Given that these medical conditions have been reported and described, could venipuncture be a cause of sudden unexpected death in children? To our knowledge, there have been no reports to prove that venipuncture/phelobotomy can definitely be the sole cause of death. However there have been reports that suggest an association between them, as well as studies regarding needle phobia, BHS and RAS that suggest that venipuncture may lead to a critical condition or state due to the cardioinhibitory effect of the vasovagal reaction to venipuncture [7–11]. However, these cases involved adults, a young adult and a child but not an infant. Therefore, we analyzed our cases and conducted a review of the literature regarding our cases to identify if there is a causal relationship between sudden death and venipuncture in the framework presented by the Bradford-Hill criteria [12].

Our cases and the case reports revealed a temporal relationship between sudden death and venipuncture, suggesting a possible association between them. Vasovagal reaction after noxious or unpleasant stimuli seems to occur both in infants and in adults, suggesting a possibility of consistency. Moreover, there was a biological plausibility and coherence between them. However, there is no dose-response quantitative relationship between them.

Specificity is important point in determining venipuncture as the only cause of sudden unexpected death and is relevant in determining the strength of the association. In our cases, the postmortem examination with review of scene circumstances and medical records were performed and some diseases could be identified; however, they were not enough to explain their sudden unexpected death. We speculated that a vasovagal reaction following venipuncture may worsen the pathologic conditions, eventually resulting in their deaths. However, it was not enough to explain their deaths because many pediatric patients who were admitted in a hospital and underwent venipuncture for further evaluation and treatment were discharged

without any negative outcomes. This implies that there might be an unknown pathologic substrate that makes the patients susceptible for vasovagal response. A recent genetic study on the cases of sudden infant death [13] revealed that genetic abnormality related to cardiovascular or metabolic disease would contribute to sudden death. They also suggested that electrocardiographic (ECG) screening should be performed in infancy for potential fatal arrhythmia. As a postmortem examination, it is impossible to perform ECG screening on the deceased. Genetic investigation still remains at the research level, and is not used in practice yet. Further studies are necessary in order to conclude a causal relationship.

Although our study with a review of literature is not enough to prove a causal relationship between venipuncture and sudden death, our cases suggest that if the pain related to medical procedure can be prevented or managed, it might reduce the possibilities of vasovagal reactions to noxious stimuli. Recent research revealed that infants are in neuronal development and exposure to repeated painful episodes may give rise to adverse outcomes in brain development and stress response systems, which may persist into later life [14].

In 2016, the American Academy of Pediatrics published an updated article in order to prevent and manage procedural pain in newborn infants based on new medical evidence [15]. The SickKids Hospital established a clinical practice guideline for pain management for neonates [16]. This guideline suggested that pediatricians and health care professionals who care for neonates should focus on pain prevention and management. Moreover, all infants should receive physical and psychological developmentally appropriate and strategic interventions during painful procedures, and pain management is recommended for several medical procedures including venipuncture and intravenous catheter insertion. Any similar clinical guideline has not been published yet by the Korean Medical Guideline Information Center [17].

We reviewed and analyzed our cases of sudden unexpected deaths in children after venipuncture by conducting a literature review. We could find an association between a painful medical procedure and

sudden unexpected death, but there was not enough medical evidence to prove their causal relationship. However, this study suggests that the prevention and management of pain in pediatric patients would be helpful in avoiding an adverse outcome related to extreme vasovagal response to pain in a minority of them.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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