

Papaverine Prolonging the Patency of Peripheral Arterial Catheters in the Neonatal Intensive

Care Unit

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Abstract

Critically ill infants often require long-term peripheral arterial lines to monitor blood pressures and provide access for frequent blood gas monitoring. Neonatal vessels, due to their small and delicate vasculature, are prone to vasospasms that decrease the duration of the line. Papaverine, an anti-vasospastic drug used in the adult population, has had little research conducted in the neonatal population.

Purpose: To compare the patency duration of peripheral arterial lines with papaverine to those without papaverine in the neonatal population.

Research Design & Population: A retrospective chart review was completed in the Neonatal Intensive Care Unit at Children's Hospital in Omaha, Nebraska. The study was conducted on sixty patients 25-40 weeks gestation with peripheral arterial lines between the months of June 2012 and August 2013. Line duration in days was recorded, as well as if the infant had a congenital heart defect and/or intraventricular hemorrhage.

Results: There was no statistical significance in line duration when comparing papaverine-infused peripheral arterial lines and those without papaverine.

Papaverine Prolonging the Patency of Peripheral Arterial Catheters in the Neonatal Intensive Care Unit

Critically ill and/or premature neonates often require arterial catheters to provide accurate blood pressure readings and easy access for blood sampling, especially blood gases.

Hemodynamic monitoring and frequent arterial blood gas measurements are essential in the management of the high-risk neonate due to the rapid changes that occur in the very small or extremely ill infants. There are two types of arterial lines that are used in the neonatal intensive care unit (NICU): umbilical arterial catheter (UAC) or a peripheral arterial line (PAL). The neonatal nurse practitioner (NNP) or physician usually attempts an arterial catheterization via the umbilical cord in the extremely premature or critical ill infants, but an umbilical artery cannot be catheterized in every infant. In instances where umbilical artery access is unachievable, peripheral arterial lines are placed for close monitoring. Post-operation management of neonates undergoing a surgical procedure often requires insertion of peripheral arterial lines to closely monitor blood pressure and arterial blood gases. Clinical history and experience with peripheral arterial lines show an adverse effect of vasospasm, a condition in which a blood vessel spasms, often causing vasoconstriction. This can lead to tissue ischemia and tissue death.

A typical arterial line solution includes normal saline with 1 unit per milliliter of heparin. Heparin decreases the incidence of thrombosis or clotting. Research on the use of the drug papaverine has been studied to assess its effectiveness in prolonging the patency of peripheral arterial catheters in neonates. Papaverine is a drug used for peripheral vasospasms. The most notable effect of the drug is smooth muscle relaxation, especially in the presence of spasms. Papaverine has been studied to determine its impact in prolonging the duration of the arterial line however research on its use in the neonatal population has been limited. Papaverine was first

studied in 1993 with its effect on decreasing vascular spasms in cranial arteries. In 2005, neonatal research reviewed the use of papaverine in arterial line solutions and found that continuous infusion of papaverine-containing fluids prolonged the patency of peripheral arterial catheters in neonates (Griffin & Siadaty, 2005).

It is extremely important to maintain the patency of an arterial catheter. Without an arterial catheter, close monitoring of blood pressure and/or blood gas measurements are unknown. Also, without an arterial catheter, the practitioner must frequently do a radial puncture to assess the arterial blood gas and obtain the results of the ventilator changes. Not only does this increase the risk of infection, it is a painful procedure. There is literature documenting newborn patients in the neonatal intensive care unit, when undergoing painful stress without an effective analgesic, are at risk for later cognitive, learning, memory, and attention deficits, in addition to an inability to face new situations (Vitaliti et al., 2012).

It is important to maximize the duration of the peripheral arterial line. Peripheral arteries in the neonatal population are very small and prone to vasospasm. Vasospasms can shorten the functional duration of the peripheral arterial catheters causing reinsertion of the line. This reinsertion of the arterial line increases the risk of infection and can increase other adverse events including bleeding or thrombosis. A line that clots off due to a vasospasm or thrombosis has to be reinserted at a different site. This causes the infant additional pain and may also cause increased parental anxiety and distress. Frequent peripheral arterial punctures can increase the risk of infection, bleeding, and thrombosis in neonates. Catheter-related bloodstream infection is one of the most common nosocomial infections in the NICU. Risk factors include frequency of invasive procedures and altered skin integrity. Healthcare associated infections are still the major source of morbidity and mortality in NICU (Wu & Mu, 2010).

The duration of peripheral arterial lines needs to be maximized in the neonatal intensive care unit to decrease painful procedures and nosocomial infections. Papaverine has been used in peripheral arterial lines to reduce vasospasm, which in turn decreases the frequency of arterial punctures and reinsertion of the line. The purpose of the proposed scholarly project is to conduct a retrospective review to compare the patency duration of peripheral arterial lines without papaverine-and those with papaverine in high-risk neonates in the NICU.

Review of the Literature

The aim of this review was to examine the clinical effects of the drug papaverine in reducing vasospasm and prolonging the duration of a peripheral arterial line. Frequency of invasive procedures to neonates can cause prolonged pain, an increase in bleeding and thrombosis, and an increase in infection rates. The intention of this review was to compile existing research so far obtained, to contribute to existing knowledge, and help researchers and health care providers find sufficient evidence for the use of papaverine in prolonging the patency and duration of peripheral arterial lines in the NICU.

Peripheral Arterial Line Risks

As advances in neonatology are becoming more profound, vascular catheters are essential in the resuscitation and management of critically ill infants. Peripheral arterial catheters are at high risk for thrombosis and vasospasm, which in turn increases the instance of discontinuing the line and reinserting a new one. Frequency of invasive procedures and contact with healthcare workers expose newborns to high risks of infection. A catheter-related bloodstream infection is one of the most common and deadly nosocomial infections in the NICU (Wu & Mu, 2010). Repeated invasive procedures in neonates can alter their subsequent pain processes, long-term development and behavior (Carbajal et al., 2008). Carabajal et al. studied 430 neonates with a

mean gestational age of 33 weeks and collected data on painful procedures in the NICU upon admission. They found that neonates experienced 60,969 first attempt procedures with 69 percent of these painful and 30 percent stressful. Subsequent procedural attempts accumulated to 11,546 in which 89 percent were painful and 10 percent stressful (Carbajal et al., 2008).

Papaverine

Review of the current literature on the use of papaverine in the Neonatal Intensive Care Unit is very limited and the Federal Drug Administration has not approved the drug for safe use in neonates. Papaverine relaxes the smooth musculature of larger blood vessels, especially coronary vessels, systemic peripheral vessels, and pulmonary arteries. The vasodilatory effect is thought to be related to its ability to inhibit cyclic nucleotide phosphodiesterase, thus increasing levels of intracellular cyclic AMP. Papaverine increases cerebral blood flow and decreases cerebral vascular resistance. It is metabolized in the liver and excreted in the urine in an inactive form (Young & Mangum, 2011). The continuous infusion of papaverine is used in peripheral arterial lines to reduce vasospasm and prolong duration of the line. Neonatal papaverine infusions are prepared by mixing 30mg/ml of the drug with a 250ml solution of standard peripheral arterial line, such as 0.9 or 0.45 percent sodium chloride (Bell, 2008). Caution is warranted in very low birth weight infants in the first days after birth due to the potential of developing or worsening intracranial hemorrhage. Chronic hepatitis has also been reported in the adult population (Young & Mangum, 2011).

Papaverine Use

Papaverine's use has been indicated for many other vascular spasms, including smooth muscle spasms in myocardial infarctions, angina, erectile dysfunction, peripheral and pulmonary embolism, peripheral vascular disease, cerebral angioplasty states, and visceral spasms. Its

unlabeled indications include the prevention of vasospasm during the harvesting of mammary arteries for coronary artery bypass graft surgery. Papaverine use has also been effective to prevent loss of the femoral artery pulse in pediatric cardiac catheterization (Lexicomp, 2013). Approximately 30 percent of adult patients who survive a cerebral hemorrhage are affected by vasospasm (Milburn et al., 1998). Papaverine has shown a complementary role with angioplasty for treating vasospasm in cerebral vessels. (Milburn et al. 1998) found that papaverine causes vasodilatation in cerebral arteries, in turn improving cerebral blood flow and preventing infarction in these patients.

Papaverine Use in Neonates and Pediatrics

Heulitt and Farrington first studied papaverine in the pediatric population in 1993. Children between the ages of 3 weeks and 18 years at Dallas Children's Hospital were admitted into this study if they had an indwelling peripheral arterial catheter inserted during hospitalization. A sample size of 200 subjects was used and randomly assigned to two groups: peripheral arterial lines with continuous papaverine infusions and a placebo group without papaverine. Although infants in this study were greater than 3 weeks of age, Heulitt & Farrington (1993) stated that neonates, especially those neonates born prematurely, are at a relatively high risk for an increase in intracranial bleeding by papaverine-induced cerebral vasodilatation and providers should use caution when prescribing papaverine to this population. According to Heulitt & Farrington (1993), catheter failure was defined as either an inability to draw blood from the catheter or the loss of waveform. The study concluded that papaverine reduced the arterial catheter failure and its vasodilatory effect reduced catheter-induced vasoconstriction, preventing thrombosis distal to the catheter.

Griffin and Siadat studied papaverine use in peripheral arterial lines in the neonatal

population in 2005. A randomized, controlled trial of 82 catheters placed in 70 neonates in a papaverine group was compared with 98 catheters placed in 71 neonates in a placebo group. The study found that the papaverine infusion significantly prolonged the duration of the catheter. The longest catheter duration in the papaverine group was 44 days versus 27.6 days in the placebo group. There were no indications of increased intraventricular hemorrhage however the study did warrant caution when using papaverine with extremely premature infants (Griffin & Siadaty, 2005).

Research has stated that papaverine is noted to be an effective anti-vasospastic and vasodilatory drug to reduce vasospasms in arteries. It has been noted that there is a shortage of experimental studies addressing the anti-vasospastic effect of papaverine in peripheral arterial lines in the neonatal population. Continuous infusions of papaverine in peripheral arterial lines have shown a promising outlook in decreasing line failure rates. The literature suggests that more similar methodological research is needed to confirm the use of papaverine in the neonatal population is safe and effective and the exact risk of intraventricular hemorrhage in extremely premature infants.

Theoretical Framework

The physiologic framework was used for this study. Understanding of the normal physiology is essential to understand the uses of papaverine and its effects on the circulatory system and clotting.

Arteries carry blood from the heart to the rest of the body. Arterial walls are composed of three types of tissues: elastic connective tissue, fibrous connective tissue, and smooth muscle. Peripheral arteries are labeled as muscular arteries, or medium sized and smaller arteries that are further from the heart. The function of the peripheral arteries is to bring blood to other parts of

the body. They also help control blood flow as their smooth muscle fibers are stimulated to contract as in vasoconstriction, or relax in vasodilation (McCance & Huether, 2010).

Peripheral arterial catheters are inserted into peripheral arteries to monitor arterial blood pressures and provide access for frequent arterial blood sampling. These catheters are usually placed in the radial, ulnar or post-tibial artery. Vasospasm is a common side effect of peripheral arteries after cannulation has occurred. Normal endothelial cells release nitric oxide and prostacyclin, which cause the relaxation of smooth muscle cells (vasodilation) and reduce aggregation of platelets. This introduction of a catheter down-regulates the release of these vasodilatory substances. During vasospasm, a dysfunctional endothelium does not stimulate as much prostacyclin and nitric oxide to induce smooth muscle relaxation (Vanhoutte, Shimokawa, Tang, & Feletou, 2009). The presence of catheters in a peripheral artery can also cause damage to the endothelium and introduce a foreign surface with thrombogenic properties. Infants are more prone to thrombosis because of their underdeveloped clotting mechanisms, small vessel diameter, and critical underlying diseases. Aggregation of platelets around the catheter can stimulate thromboxane A₂ and serotonin, causing the contraction of smooth muscle in the artery, otherwise known as vasospasm (Hermansen & Hermansen, 2005).

The use of continuous infusions of papaverine has been shown to decrease peripheral vasospasm and increase duration of the peripheral line. Papaverine directly relaxes the tone of smooth muscle, especially when the muscle has been spasmodically contracted. The vasodilatory effect of the drug may be related to its ability to inhibit cyclic nucleotide phosphodiesterase, thus increasing levels of intracellular cyclic AMP. Papaverine also increases cerebral blood flow (Young & Mangum, 2011).

Peripheral artery vasospasm and occlusion is a very serious complication of peripheral

arterial lines. A decreased arterial blood flow to the affected limb can deprive the tissue of its essential components to survive. Eventually, lack of blood flow will cause the tissue to become ischemic and die.

Methods

Research Design, Population Sample & Setting

The methodological approach to this study was a retrospective chart review. Infants eligible for the study were those infants who were admitted to the Children's Hospital and Medical Center surgical NICU between June of 2012 and August 2013 and who required insertion of a peripheral arterial catheter. The arterial lines were used for frequent arterial blood pressure and blood gas monitoring. Papaverine was used in every peripheral arterial line since 2000 at Children's Hospital and Medical Center. A nation-wide shortage of papaverine caused a discontinuation of the medication in December of 2012. Subjects were grouped based on the contents of the continuous infusion through the peripheral arterial line. All participants had continuous infusions of fluid through the peripheral arterial line: normal saline with heparin, half normal saline with heparin, or sodium acetate with heparin.

Measurement Methods & Data Collection Procedures

Two groups were studied for this research. A group of thirty infants with papaverine-containing solutions were compared to a control group of thirty infants who did not receive papaverine. Chart reviews took place over six months in each of the groups. Participants were included in the study if their gestational age was between 25 to 40 weeks of gestation, and their charts revealed the use of a peripheral arterial line. The charts were reviewed for line duration and any complications. The main outcome measure was peripheral arterial line duration in days. It was also noted if the patient had congenital heart disease or an intraventricular hemorrhage

before and after papaverine administration. Catheter failure is defined as an arterial line with an absent wave form and/or an arterial line that is unable to draw. The reason for line removal was noted in the data collected. The reasons were elective discontinuation, leaking, non-functioning (no wave form or unable to draw), accidental dislodgement, or compromised perfusion.

Data Analysis

Data were gathered from the control group and the placebo group. An independent samples t- test was used for statistical data analysis to evaluate the relationship between the two groups. Primary outcome measure was line duration in days. An independent t-test was also performed to identify any correlation between congenital heart disease and line duration. Descriptive tests were completed on all other data, including intraventricular hemorrhage and reasons for discontinuing the arterial line.

Ethical Considerations

The neonatal population is a vulnerable population and ethical considerations include protecting the safety and ethical rights to each patient respectively. The right to privacy and anonymity were maintained for the participants in this study. Papaverine has potential side effects of causing IVH in extremely premature infants; therefore, this study only involved a chart review of the infants that had already received the medication as prescribed by the neonatologist.

Limitations

This study was confined to a surgical neonatal intensive care unit and sample size is relatively small. Patients in this unit were likely to have undergone surgery and were likely to be patients with congenital heart disease. In such circumstances, vasculature in these infants may be abnormally developed compared to the vasculature of a healthy infant.

Results

Gestational age at the time of insertion of the peripheral arterial line ranged from 23 weeks to 61.71 weeks. An independent-samples t-test was conducted to compare line duration of peripheral arterial lines when using continuous infusions of papaverine compared to lines without papaverine. There was no significant difference in line duration with papaverine ($M=5.5$, $SD=4.2$) than without papaverine ($M=4.5$, $SD=4.2$, $p=.307$, $df=58$). Nineteen out of 21 patients had congenital heart disease. An independent-samples t-test was conducted to compare patients with congenital heart disease and line duration. There was no significant difference in line duration in patients with congenital heart disease and those without heart disease ($p=.891$, $df=58$). Intraventricular hemorrhage was assessed after the papaverine infusion and three patients had an increase in IVH after papaverine use. The reason for discontinuing the arterial line was also assessed using the five categories mentioned previously. The group without papaverine reported 46 percent elective discontinuation, 43 percent non-functioning, 3 percent leaking, and 6.7 percent accidental dislodgement. On the contrary, the papaverine group had 46 percent removed electively, only 20 percent non-functioning, 20 percent leaking, 6.7 percent accidental dislodgement, and 6.7 percent with compromised perfusion (see Table 1).

Table 1.1

Reason for Discontinuing PAL			Frequency	Percent	Valid Percent
Papaverine					
No Papaverine	Valid	elective	14	46.7	46.7
		non-functioning (no waveform or draw)	13	43.3	43.3
		leaking	1	3.3	3.3
		accidental dislodgement	2	6.7	6.7
		Total	30	100.0	100.0
Papaverine	Valid	elective	14	46.7	46.7
		non-functioning (no waveform or draw)	6	20.0	20.0

leaking	6	20.0	20.0
accidental dislodgement	2	6.7	6.7
compromised perfusion	2	6.7	6.7
Total	30	100.0	100.0

Discussion

The literature review revealed that papaverine may increase peripheral arterial line duration in the neonatal population. Using the evidence mentioned above in this study, we cannot conclude that using papaverine in peripheral arterial lines will significantly increase the duration of the line. However, a peripheral arterial line with papaverine lasted on average one day longer than a line without papaverine. With a larger sample, these findings may indicate statistical significance. Although the t-test did not show statistical significance in this study, an increase in line duration by one day is clinically significant for reducing frequent painful procedures and sepsis in the extremely premature infant. Line duration did not seem to be impacted by infants with congenital heart disease and also did not further intraventricular hemorrhage in patients with previous intraventricular hemorrhage before papaverine infusion. It can be noted that the non-papaverine group had a higher incidence of line discontinuation due to a non-functioning line (40%) as compared to the papaverine group (20%). This may indicate that papaverine did indeed increase line patency and could possibly increase line duration days with a larger sample (see table 1.1).

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