CASE REPORT

Sodium nitroprusside, a lifesaving treatment for neonatal hypertension: an Irish experience

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Accepted 14 March 2018

SUMMARY

We present a 30+2-weeks-old (30 weeks and 2 days) male, twin 1, born by emergency caesarean section due to twin-twin transfusion syndrome (absent end-diastolic flow and cardiac anomaly in twin 2) presenting with hypertensive crisis on day 3. He was already on milrinone and propranolol. His echocardiogram showed poor left ventricular contractility and after cardiology consultation received sodium nitroprusside, which eventually saved his life by decreasing his blood pressure and improving cardiac function. As sodium nitroprusside is very rarely used for hypertensive crisis in neonates, we would like to share our experiences on dosage, challenges in administration due to its fast onset of action, criteria for monitoring for complications and finally weaning. Baby developed severe bilateral periventricular leukomalacia as a potential complication of hypertensive crisis, preceded by bilateral periventricular flare secondary to twin-twin transfusion.

BACKGROUND

- Studies have shown that milrinone can be used successfully to treat hypertensive crisis, but in our case baby developed crisis when already on milrinone. So we had to think of another stronger drug to reduce the crisis as early as possible.
- First case to be reported in Ireland where sodium nitroprusside is used for antihypertensive crisis in a preterm neonate.
- Difficulties witnessed in managing systemic hypertension with routine antihypertensive medications.
- Limited information available on preparation, monitoring and adverse effects of sodium nitroprusside.
- Neonatal hypertensive crisis can cause potential life-threatening complications if not treated early.

CASE PRESENTATION**Gestation**

Thirty weeks and two days; recipient: twin 1.

Mode of delivery

Born by emergency section.

Reason for emergency section

Due to twin-twin transfusion syndrome (monochorionic diamniotic), hypoplastic arch and

polyhydramnios (absent end-diastolic flow and aneurysmal patent ductus arteriosus and hypoplastic left pulmonary artery in twin 2).

Birth weight was 1.87 kg.

Maternal details

Thirty years old, American/Irish, O positive, serology negative, rubella immune, no septic risk factors.

Birth history

He had suctioning and received 2 min of IPPV as his heart rate was 80. He was transferred to neonatal intensive care unit on transport incubator on nasal continuous positive airway pressure (NCPAP). Apgars were 8 at 1 and 9 at 5.

Respiratory

After initial CPAP, he was later intubated and ventilated with pressure control, assisted control volume guarantee for 44 hours and extubated to nasal bilevel CPAP (BiPAP). He was on BiPAP for next 36 hours, where he was changed to NCPAP for another 34 hours. He had spontaneous respiration in room air on day 5.

Cardiovascular

Day 1 echocardiogram showed hypoplastic transverse arch, no coarctation, severe biventricular hypertrophy. On day 3, when he was already on 0.2 µg/kg/hour of milrinone, slowly increased to 0.4 µg/kg/hour, he developed consistent high blood pressure (BP) needing propranolol 1 mg three times a day, and on day 4, he developed BP of 112/72, MAP 88 with left ventricular dysfunction (poor contractility) on echocardiogram, needing sodium nitroprusside (SNP) at 1 µg/kg/min, which was later raised to 2 µg/kg/min and then to 3 µg/kg/min. His milrinone was increased to 0.6 µg/kg/hour. His SNP was gradually reduced slowly at 0.2 µg every 2 hours and stopped on day 7. His methemoglobin was normal. His milrinone was weaned off slowly and stopped on day 7. However, he continued his propranolol for 6 weeks until corrected, as his day 10 echocardiogram showed biventricular hypertrophy with dynamic obstruction. Day 14 echocardiogram showed severe concentric left ventricular hypertrophy with mid cavity obstruction, right ventricular concentric hypertrophy with midcavity obstruction, mild dysplastic pulmonary valve. On day 28, concentric left ventricular hypertrophy

To cite: Deliu AG, Sanneerappa PBJ, Franklin O, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-221856

with midcavity obstruction persists with hyperdynamic left ventricular function, indicating upper limit of normal. Mild dysplastic pulmonary valve persists. He was advised to continue propranolol 1 mg/kg three times a day until Out Patient Department (OPD) in 2 months.

Renal

Normal renal ultrasound with no suggestive evidence of renal artery stenosis and normal urea and creatinine.

Neurology

Good tone, normal reflexes, head circumference normal.

Gastrointestinal

Trophic feeds started on day 4, stopped on day 5 until day 6. He was on full feeds on day 10.

Mirobiology/Infections

Initial blood culture and further routine methicillin-resistant *Staphylococcus aureus* (MRSA) screens negative.

Eyes

No retinopathy of prematurity;
Home on day 31;
Still had 2/6 systolic heart murmur;
Feeds: 150 mL/kg of oral nutriprem 2, 4 hourly;
Weight: 2.79 kg (75-91st centile);
Head circumference: 34.2 cm (91st centile).

INVESTIGATIONS

Haematology

- ▶ Full blood count: no thrombocytopaenia or neutropaenia;
- ▶ Coagulation screen: normal.

Biochemistry

- ▶ Liver function test;
- ▶ Developed hyponatraemia on day 5 (sodium of 123);
- ▶ Urea and electrolytes;
- ▶ Bone profile, vitamin D;
- ▶ Methemoglobinaemia: all normal;
- ▶ Urine for vanillylmandelic acid: negative.

Metabolic workup

- ▶ Acylcarnitine, free carnitine, serum amino acids: normal.

Microbiology

- ▶ Blood culture for culture and sensitivity: negative at 36 hours.

Radiological

Echocardiogram

- ▶ Day 1: hypoplastic transverse arch, no coarctation, severe biventricular hypertrophy;
- ▶ Day 4: left ventricular dysfunction (poor contractility);
- ▶ Day 10: biventricular hypertrophy with dynamic obstruction;
- ▶ Day 14: severe concentric left ventricular hypertrophy with midcavity obstruction, right ventricular concentric hypertrophy with midcavity obstruction, mild dysplastic pulmonary valve;
- ▶ Day 28: concentric left ventricular hypertrophy with midcavity obstruction persists with hyperdynamic left ventricular function, indicating upper limit of normal. Mild dysplastic pulmonary valve persists.

Cranial ultrasound

- ▶ Day 1: bilateral periventricular echogenicity;
- ▶ Day 4: same finding;
- ▶ Day 26: extensive periventricular leukomalacia.

Renal ultrasound

- ▶ No renal artery stenosis; normal corticomedullary differentiation. There was no evidence by renal ultrasound to suggest renal artery stenosis; however, renal arteriography would be a challenging investigation.

Genetic workup

- ▶ Microarray: normal male (arr(1-22)×2, (X, Y) ×1).

DIFFERENTIAL DIAGNOSIS

1. Pheochromocytoma;
2. Renal artery stenosis;
3. Renal vein thrombosis.

TREATMENT

- ▶ Milrinone;
- ▶ Propranolol;
- ▶ Sodium nitroprusside;
- ▶ Oral sodium supplements;
- ▶ Antibiotics: benzyl penicillin and gentamycin.

OUTCOME AND FOLLOW-UP

BP slowly returned to normal within 6 hours of starting SNP and it was slowly weaned off during the next 3 days. Cranial ultrasound showed the baby developed severe periventricular leukomalacia on day 26. He was discharged on propranolol with intense neurophysiotherapy follow-up.

On his term check, he was confirmed to enable Ireland for integrated occupational and neurophysiotherapy. Weight was 4.2 kg plotting on 75th–91st centile, head circumference was 37 cm (91st centile), happy with progress and referred to neurology.

At 6 week corrected age check weight was 5.5 kg and head circumference was 39 cm, normal developmental check. He was returned to normal formula feeds. His BP was normal. Follow-up with the Enable Ireland team and 4/12 with us.

DISCUSSION

Neonatal hypertension is very rare. It is defined as a systolic BP more than 95 percentile for infants of similar size, gestational age and postnatal age.¹ It has been shown that about 0.2% to 3% babies (both term and preterm) develop arterial neonatal hypertension during their care in an NICU and umbilical catheterisation.² The prevalence of babies requiring intensive care is gradually increasing.³ Although its incidence is rare, mortality and morbidity associated with neonatal hypertension could be very serious due to end-organ damage, which includes hypertensive retinopathy, left ventricular hypertrophy, cardiomyopathy and encephalopathy.⁴

There are many causes for neonatal hypertension. Of which, renal artery occlusion is the most common cause. It could be secondary to congenital stenosis or thrombosis postumbilical catheter insertion to renal artery.

Few other causes include congenital causes like rubella infection, renal dysplasia and structural anomalies causing obstruction to the urinary system. It could also be due to acute renal injury causing acute tubular or cortical necrosis and nephritis. Non-renal causes include cardiac causes like aortic calcification or coarctation, patent ductus arteriosus, neurological causes like

cerebral bleed, seizures, intraventricular haemorrhages or endocrine causes like congenital adrenal hyperplasia, hyperaldosteronism, hyperthyroidism and pheochromocytoma.⁵

Clinical features of neonatal hypertension are very non-specific. It can range from mild subjective symptoms like poor feeding, lethargy, agitation to prominent objective symptoms of tachypnoea and tachycardia.⁵ It is very important to remember that it could also present very rarely with circulatory failure secondary to hypertensive crisis.⁶

As neonatal hypertension can cause very severe complication to target ends, it is very important to recognise it early and treat with appropriate medications so that future disabilities can be minimised.

In a study by Louw *et al*,⁶ it is clearly shown that left ventricular dysfunction and mild aortic regurgitation was observed in five of the six cases (83%) with neonatal hypertensive crisis with circulatory shock, which was seen in our baby. Another baby had apical thrombus as a cause for hypertensive crisis. This same study also showed neonatal hypertensive crisis can be treated successfully with intravenous milrinone therapy to see rapid improvement of the clinical condition. In our case, we used sodium nitroprusside, which reversed the hypertension crisis rapidly and stabilised the blood pressure. However, our baby developed extensive periventricular leukomalacia which is poorly understood and could be probably due to initial insult as a recipient in twin-twin transfusion and later an insult with sudden idiopathic hypertensive crisis.

In another case report by Vesoulis *et al*⁷ it was about a 35-week preterm who was initially treated with labetalol and sodium nitroprusside for idiopathic hypertension, used minoxidil as an oral medical for long-term treatment. However due to anorexia, minoxidil was discontinued.

After initial medical treatment, further surgical interventions are considered to either reverse neonatal hypertension like repair of aortic coarctation, renal artery obstruction, polycystic kidney disease, tumours or to decrease the long-term use of medical treatment such as ureteral obstruction.⁵

Previously, Milou *et al*⁸ and McBride *et al*⁹ have narrated the use of nicardipine and hydralazine in treatment of neonatal hypertension in 2000 and 2003, respectively.

Tinker and Michenfelder¹⁰ explained that sodium nitroprusside is a very potent vasodilator. It is considered to be very effective and is readily reversible. He further described it as a very strong vasodilator and acts by reducing the afterload and improves myocardial dysfunction. The onset of action is almost immediate within 1–2 min. Benitz *et al*¹¹ used sodium nitroprusside in neonates describing its efficacy and safety.

Initial dose was between 0.5 and 1.5 µg/kg/min. The dose can be gradually increased by 0.5 µg/kg/min every 2 to 3-hour interval to a maximum dose of 4.0 µg/kg/min and slowly weaned off at the same rate to 1 µg/kg/min before discontinuing it.

It is very important to monitor levels as they are metabolised by haemoglobin into cyanide, which in turn is partly detoxified by kidneys and liver to thiocyanate, and thus frequent monitoring would prevent fatal complication of cyanide poisoning. We have to note that either thiocyanate or cyanide levels in the blood do not indicate the true extent of free cyanide. So, we should also monitor toxicities by monitoring metabolic acidosis and elevated lactate levels. Sodium nitroprusside's side effects include hypotension and cyanide toxicity, which could be fatal, so it should be monitored promptly. Thomas *et al*¹² explained about cyanide toxicity from sodium nitroprusside. Hottinger *et al*¹³ also explained about coronary steal phenomenon and

increased cranial hypertension as associated side effects in their clinical concept review article.

In case of sodium nitroprusside-induced cyanide poisoning, a combination of sodium thiosulfate and sodium nitrite was the only approved treatment by the Food and Drug Administration, as reported by Zerbe and Wagner.¹⁴

CONCLUSION

Neonatal hypertension is very rare and neonatal hypertensive crisis is even rarer. Due to life-threatening complications associated to target organs, appropriate antihypertensive medication has to be chosen and administered early to prevent or reduce serious debilitating conditions. Sodium nitroprusside can be considered in hypertensive crisis if a neonate is already on milrinone. Due to serious side effects of cyanide poisoning, monitoring thiocyanide levels with metabolic acidosis and lactate is very crucial. Hypertensive crisis in a neonate can cause severe periventricular leukomalacia in a previously susceptible neonate.

Learning points

- ▶ On echocardiogram, a structurally normal heart with left ventricular dysfunction in a neonate, consider hypertensive crisis as an underlying cause.
- ▶ Treat neonatal hypertension early, as it can cause severe damage to target organs.
- ▶ In refractory hypertension in a preterm, already on a beta blocker or milrinone, consider sodium nitroprusside.
- ▶ Monitor the side effects of sodium nitroprusside which include hypotension and cyanide poisoning, which could be fatal if not recognised and treated early.
- ▶ Consider surgical intervention to reverse the structural causes of neonatal hypertension.

Acknowledgements Special thanks to Brian Cleary, Clinical Pharmacist, Rotunda Hospital, Ireland, Prof Afif El Khuffash, Consultant Neonatologist, Rotunda Hospital, Dublin, Ireland and Prof Andrew Green, Consultant Geneticist, Children's University Hospital, Temple Street, Dublin. All staff of Rotunda Hospital.

Contributors AGD and PBJS were both involved very closely in observing baby vitals closely and delivering treatment, collecting patient consent, primary PubMed search to find out more about sodium nitro prusside drug and relevant publications, collecting and reviewing case reports. PBJS was involved in writing the initial script. Discussion and references were discussed with JL until finalisation. OF specialist cardiology input regarding treatment and further management. JL supervised overall treatment and gave guidance to finalise the case report and to the final editing.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors

Competing interests None declared.

Patient consent Parent consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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