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Original Article

Foetal supraventricular tachycardia with hydrops fetalis: a role for direct intraperitoneal amiodarone

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Abstract *Introduction*: Persistent foetal tachyarrythmias complicated by hydrops fetalis carry a poor prognosis, with foetal death reported in excess of a quarter despite treatment. We present our experience with direct intraperitoneal amiodarone administration in eight hydropic foetuses with resistant supraventricular tachycardia. *Methods*: Amiodarone was injected slowly into foetal peritoneal cavity under ultrasound guidance. All mothers were loaded with oral amiodarone before the procedure and maintained on it. The procedure was repeated guided by foetal rhythm. *Result*: All eight cases had severe hydrops with a median foetal heart rate of 255 bpm (range 240–300 bpm), and the median gestational age was 27^{+1} weeks (range 21–33^{+3} weeks) at presentation. In six cases, the average time for supraventricular tachycardia to revert to sinus rhythm from the first procedure was 11.5 days. In one case, intravascular injection of amiodarone into the umbilical vein was performed before intraperitoneal injection, which resulted in conversion to sinus rhythm sustained until delivery. In the last case, supraventricular tachycardia and severe hydrops persisted and the baby was delivered 5 days later at 34 weeks' gestation. Hydrops resolved in five foetuses with a mean resolution time of 28.4 days. The mean gestational age at delivery was 34^{+5} days and seven of eight cases survived beyond the neonatal period with good postnatal outcomes. *Conclusion*: Intraperitoneal administration of amiodarone is a relatively simple and effective strategy in refractory supraventricular tachycardia complicated by severe hydrops. The intraperitoneal route assures delivery of the drug to the severely hydropic foetus and enables a bolus dose to be delivered for sustained absorption.

Keywords: Intraperitoneal; foetal; supraventricular tachycardia

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Foetal tachyarrhythmias occur in ~0.5% of all pregnancies and are most frequently of supraventricular origin, with atrioventricular re-entry tachycardias and atrial flutter being the predominant mechanisms.[1] Sustained foetal tachycardia may lead to intrauterine congestive heart failure and hydrops fetalis, which is associated with significant mortality or severe neurologic morbidity in survivors.[2–4]

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The management of foetal tachycardia with respect to the type of drug or combination of drugs to use and the optimal route of administration remains debated. Digoxin is commonly used as first-line transplacental treatment in non-hydropic foetuses, although some centres prefer the use of flecainide and sotalol. In the presence of hydrops fetalis, flecainide and amiodarone are often the drugs of choice.[2] When transplacental treatment fails to restore sinus rhythm or reduce foetal heart rate, direct foetal treatment has been used to deliver the drug directly to the foetal compartment. Several modes of foetal administration of antiarrhythmics have been described including the intra-umbilical, intramuscular, and intraperitoneal

routes. However, limited data are available to draw conclusions on their efficacy.[2,3,5–8]

The aim of this retrospective study was to review the prenatal management and outcomes of a series of eight hydropic foetuses with supraventricular tachycardia treated with direct intraperitoneal injection of amiodarone.

Methods

Cases of foetal supraventricular tachycardia with hydrops treated with intraperitoneal amiodarone between 1996 and 2011 were identified from an electronic database at a tertiary referral centre. The maternal and neonatal case notes were reviewed to ascertain the diagnosis and to follow the clinical course of these cases from presentation during pregnancy to postnatal outcomes.

Prenatal diagnosis of foetal arrhythmias is made using standard transabdominal foetal echocardiocardiography including cross-sectional, M-mode, and Doppler techniques. A simultaneous record of both ventricular and atrial contractions with a four-chamber view is used to assess the relationship of atrioventricular mechanical connection. An M-mode trace of ventricular and atrial motion demonstrates cardiac rhythm and rate. In addition, simultaneous record of Doppler waveforms at the superior vena cava and the ascending aorta is recorded to assess the relation and time intervals of the atrial and ventricular contractions. Supraventricular tachycardia was defined as a rhythm with 1:1 atrioventricular conduction at a rate of >200 bpm with little beat to beat variation.

The classic definition of foetal hydrops is excessive fluid accumulation in at least two body compartments. However, classification of the severity of hydrops has not been clearly defined. We retrospectively classified the foetuses in our series according to the ultrasound findings at first presentation. The presence of a distinct rim of ascites with or without pericardial effusion is classified as mild hydrops. Abundant ascites with free-floating intra-abdominal organs and associated with pleural effusion, scalp oedema, or pericardial effusion is classified as severe hydrops.[9] Foetal echocardiograms were performed at presentation and then regularly during treatment to assess cardiac function and progression of hydrops. The patients were admitted for monitoring of foetal heart rate during therapy by regular cardiotocography and repeated ultrasound examination in order to detect changes of cardiac rhythm as early as possible.

The choice of transplacental antiarrhythmic agent and drug doses varied over the years, according to protocols published at the time and the discretion of maternal foetal medicine specialist and foetal cardiologist. The preference at our centre is flecainide or digoxin as first-line treatment, which are given orally. The doses were variable depending on the presence or absence of hydrops and were titrated according to treatment response. Combination therapy with flecainide, digoxin, and other agents has also been used. In cases of refractory supraventricular tachycardia and severe hydrops, the mothers were given the standard adult oral loading dose of amiodarone (200 mg TDS), and foetal intraperitoneal amiodarone is initiated. The foetuses were given amiodarone directly via the intraperitoneal route at a starting dose of 4–7 mg/kg estimated foetal weight plus 25% for placental circulation. This technique involves ultrasound-guided insertion of a needle into the ascites within the foetal peritoneal cavity between the umbilicus and the bladder. The amiodarone infusion is given slowly over 5–10 minutes under continuous ultrasound observation of the foetal heart rate. The procedure was repeated as necessary guided by foetal rhythm and the dose of intraperitoneal amiodarone was increased up to 10 mg/kg. The transplacental antiarrhythmics previously started were maintained throughout the pregnancy and adjusted according to response. Oral amiodarone was gradually weaned because of its potential to cause side effects in the foetus.

All mothers were admitted for maternal observations and monitoring of the foetal heart rate during therapy by regular cardiotocography and repeated ultrasound examination to detect changes of cardiac rhythm as early as possible. Foetal echocardiogram was performed daily or on alternate days until conversion to sinus rhythm. Decision for further intraperitoneal doses is guided by the proportion of time the foetus remains in supraventricular tachycardia recorded on cardiotocography in the ward, the rhythm at the time of echocardiogram, and the severity of hydrops. When sinus rhythm is achieved and maintained, foetal echocardiogram is performed every few days. Foetal drug levels were performed in some cases. Serum thyroid function test in the mothers were performed during pregnancy and in all neonates after birth.

Results

During the 15-year study period, eight foetuses were treated with direct intraperitoneal amiodarone. The median gestational age at presentation was 27^{+1} weeks (range 21–33^{+3} weeks). All eight cases had severe hydrops, with a median foetal heart rate of 255 bpm (range 240–300 bpm) at the first foetal ultrasound scan after referral. The foetal cardiac anatomy was normal and atrioventricular re-entry tachycardia was diagnosed in all cases. There were no associated structural foetal anomalies.

The prenatal management and outcome for the eight foetuses are summarised in Table 1. Transplacental antiarrhythmics were given as first-line treatment before

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Table 1. Antenatal treatment and progress of foetal SVT associated with severe hydrops.

Case No	Gestation at presentation (weeks $^{+\text{days}}$)	Initial transplacental medication	Direct foetal amiodarone treatment	Time to conversion SR post direct foetal treatment (days)	Time to in utero resolution of hydrops (days)	Gestation at delivery (weeks $^{+\text{days}}$)
1	21	D, F, P	IP	7	21	39
2	29	Am	IP	9	Unresolved	30^{+4}
3	28	F	IP	18	42	34
4	25	D, F	IP and IV	0	39	36
5	26^{+5}	D, F	IP	28	Unresolved	32^{+4}
6	33^{+3}	F	IP	na*	Unresolved	34
7	29^{+6}	F	IP	4	41	36^{+5}
8	26^{+3}	F	IP	3	19	35^{+1}

Am = amiodarone; D = digoxin; F = flecainide; IP = intraperitoneal; IV = intravascular; P = procainamide; SVT = supraventricular tachycardia
*Delivered at 34 weeks' gestation

decision for direct foetal treatment in all except case 2. The median time from commencement of first-line treatment to direct foetal therapy with amiodarone was 7 days (range 2–36 days). There is a trend for earlier consideration and institution of foetal intraperitoneal amiodarone in the later years likely related to increasing experience and operator expertise. All mothers were loaded with oral amiodarone within 24 hours before fetal intraperitoneal amiodarone. The exception was case 2 who presented with a foetal heart rate of 280 bpm and maternal preeclampsia. Foetal ultrasound showed no foetal movements and severe foetal hydrops with bilateral pleural effusions, pericardial effusion, and severe ascites. This was thought to be a case of mirror syndrome, which is associated with a substantial increase in perinatal mortality and maternal complications.[10] In addition, transplacental transfer of drug is significantly limited by severe hydrops in this case. Therefore, a decision was made for urgent direct foetal therapy with amiodarone in conjunction with maternal amiodarone. The foetus converted to sinus rhythm 9 days later after two doses of intraperitoneal amiodarone. However, the hydropic baby was delivered by emergency caesarean section at 30^{+4} weeks because of deterioration of cardiotocograph and foetal compromise but was in sinus rhythm at birth. In the earlier part of the study period, one foetus also received direct intravascular amiodarone before intraperitoneal injection at the physician's discretion. Although rapid cardioversion is desirable, the intraumbilical route is more invasive and carries a high risk of cord injury.

In six cases, successful cardioversion was achieved after initiation of intraperitoneal amiodarone. The number of intraperitoneal injections required to maintain sinus rhythm varied according to therapeutic response. Two foetuses received only one dose, another three received up to four doses, and one foetus had a total of 11 injections. The average time for supraventricular tachycardia to revert to sinus rhythm from the first procedure was 11.5 days. On the other hand, immediate cardioversion was observed in one case (case 4) when intravascular injection of amiodarone into the umbilical vein was performed before intraperitoneal injection. The foetus converted to sinus rhythm at the end of procedure, which was sustained until delivery. The remaining case (case 6) had persistent supraventricular tachycardia and severe hydrops despite two doses of intraperitoneal amiodarone. The baby was delivered 5 days later at 34 weeks' gestation as the benefit of postnatal treatment was felt to outweigh intrauterine treatment at this gestation. Hydrops resolved in five of eight fetuses, with a mean resolution time of 28.4 days.

Of the eight cases, seven survived beyond the neonatal period with good outcomes, as shown in Table 2. The mean gestational age at delivery was 34^{+5} weeks. At birth, two newborns had supraventricular tachycardia, which persisted throughout their clinical course in the neonatal intensive care unit requiring multiple antiarrhythmics. There were two neonates who were in sinus rhythm after birth but had recurrence of supraventricular tachycardia, which was intermittent and well controlled on a single drug. There were three neonates who had normal sinus rhythm at birth and no recurrence of supraventricular tachycardia in the neonatal period. However, they were started on antiarrhythmic electively at hospital discharge, which was weaned by 6–12 months at follow-up. There was one neonate (case 2) in whom in utero conversion to sinus rhythm was achieved who died on day 51 because of complications of severe hydrops and multi-organ failure, after withdrawal of care.

The postnatal ECG showed evidence of pre-excitation in 50% of cases. The thyroid function was normal in five of seven neonates and two had transient hypothyroidism requiring short-term thyroxine replacement. At the time of study, the mean age at follow-up or at discharge of the seven cases was 5.14 years (range 16 months to 11 years). In all, six children are off medications and free of supraventricular tachycardia; one child remains on

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Table 2. Postnatal outcomes.

Case no.	Gestation (weeks $^{+days}$)	Rhythm at birth	Neonatal recurrence of SVT	Initial treatment	Treatment at discharge	Current status		
						Age	SVT frequency	Medication
1	39	SR	N	Nil	D	14 years 10 months	None	Nil
2	30^{+4}	SR	Y	P	na	na	na	na
3	34	SR	N	P	P	11 years 9 months	None	Nil
4	36	SR	Y	Nil	Nil	9 years 7 months	Infrequent	Nil
5	32^{+4}	SVT	Y	P	P	3 years 10 months	Infrequent	At, V
6	34	SR	Y	F, E, D	D, Am	5 years 6 months	Infrequent	At, F
7	36^{+5}	SR	N	Nil	D	6 years 9 months	None	Nil
8	35^{+1}	SR	N	Nil	P	6 years 7 months	None	Nil

Am = amiodarone; At = atenolol; D = digoxin; E = esmolol; F = flecainide; P = propranolol; SR = sinus rhythm; SVT = supraventricular tachycardia; V = verapamil

medications with infrequent episodes of supraventricular tachycardia. There were no neurodevelopmental concerns with any of the children at follow-up.

Discussion

Persistent foetal tachyarrhythmias complicated by hydrops fetalis carry a poor prognosis, with foetal death reported in excess of a quarter despite treatment.[3,7] This may be partly explained by impaired transplacental drug transfer in hydropic foetuses compared with non-hydropic newborns secondary to placental oedema and altered placental perfusion states.[7,11] At our centre, intraperitoneal amiodarone is initiated when there is absence of therapeutic response to transplacental therapy in severely hydropic foetuses. All mothers were also loaded with amiodarone to minimise diffusion of the drug from foetal compartment to maternal compartment. In our series, we used an oral loading dose of 200 mg TDS. However, more recent studies have reported the use of larger loading doses of 1600–2000 mg per day for 2–7 days, and then reduced to the lowest effective dose necessary to sustain sinus rhythm, usually 200–600 mg per day.[12–14] In selected situations, such as suspicion of mirror syndrome when prognosis is extremely poor, intraperitoneal amiodarone has been given as first-line treatment. Conversion to sinus rhythm was achieved in seven of eight cases with gradual resolution of hydrops in utero in five cases. We encountered less cases in the latter half of the review period compared with the first half, which is likely to be due to earlier recognition and treatment of supraventricular tachycardia. Nevertheless, our experience suggests that direct foetal therapy with amiodarone is effective in refractory supraventricular tachycardia and severe hydrops.

Several modes of direct foetal treatment have been reported in the literature, including intraumbilical, intraamniotic, intraperitoneal, intramuscular, and intracardiac routes to rapidly achieve high drug concentration in the foetal compartment.[5] We adopted the intraperitoneal technique pioneered by Gembruch et al,[8] which is relatively simple and safe. A needle is inserted under ultrasound guidance between the umbilicus and the bladder into the foetal peritoneal cavity, which is easily accessible when there is marked ascites. Ascitic fluid is aspirated before administering the antiarrhythmic agent and the foetal abdomen should be carefully inspected to ensure that the infusion is not distending foetal gut or bladder. The foetal heart rate is monitored continuously during the procedure to detect sustained tachy- or bradycardia which may be caused by venous obstruction from increased intraabdominal pressure. None of our cases had this complication with the small volume given each time.[15] Intraperitoneal injection is technically easier than other

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methods of direct foetal therapy at early gestational ages, when access to foetal circulation is difficult. The procedure can be repeated without any greater risk than with the first injection. In our series, one foetus received 10 doses of intraperitoneal amiodarone over a period of 3 weeks and had no complications from the procedure. In addition, the peritoneal space provides a depot for sustained release of drug, which has a longer effect compared with the intravascular route.[7,8]

The intraumbilical route allows direct access to the foetal circulation and facilitates a quicker response to therapy. The potential for foetal blood sampling is another advantage over other techniques because foetal drug levels can be measured to guide treatment. However, intravascular administration is more invasive and carries a risk of cord injury and even death.[16] If the needle is displaced and fluid transfused into Wharton's jelly, a haematoma will develop. This can occlude blood flow and lead to foetal death. Cardiac arrest and negative inotropic effects with intravascular administration of drugs have also been reported previously.[3] The half-life of drugs administered intravascularly to the foetus are substantially shorter than when the same drugs are administered neonatally.[15] Although the therapeutic effect of the drug can be achieved rapidly via direct intraumbilical injection, the duration of effect is shorter, which may necessitate a number of repeats. In our series, one foetus was first given amiodarone intravascularly before intraperitoneal injection, which achieved a successful result. The direct intravenous injection may serve to achieve rapid cardioversion, whereas intraperitoneal administration maintains the response.

Direct intramuscular injection of digoxin in the foetal buttock has also been performed in hydropic foetuses with refractory supraventricular tachycardia.[17,18] This technique appears to shorten the time to initial conversion of supraventricular tachycardia and to sustain sinus rhythm in the foetus.[17] In addition, foetal intramuscular injection has been shown to lead to more prolonged levels of digoxin, thereby reducing the cumulative number of procedures.[18] However, the propensity for haematoma formation renders this technique impractical in the long term. There is also a risk of foetal nerve damage.[15]

Published literature on the management of foetal tachycardia suggests that no antiarrhythmic agent is consistently effective and safe. Prenatal treatment failure is often encountered in cases complicated by hydrops fetalis. Digoxin is the most common first-line drug, but has limited utility in hydrops because of incomplete passage of the drug across the placenta.[11,19] Fleicainide and sotalol, on the other hand, cross the placenta easily even in foetal hydrops. Flecainide has a conversion rate of 60–80%,[3,12,20] but up to 18.5% mortality in hydropic foetuses with supraventricular tachycardia.[3,14,20,21] The arrhythmogenic effect of flecainide has been linked to poor left ventricular function, high drug concentration, and cardiac failure.[22,21] Similarly, sotalol has a success rate of 40–60% in foetal supraventricular tachycardia associated with hydrops but with up to 38% mortality.[23–25] A recent study advocated digoxin and flecainide combination therapy, which resulted in conversion to sinus rhythm or rate control in seven of eight hydropic foetuses from a cohort of 27 foetuses with foetal supraventricular tachycardia.[19] The severity of hydrops in these cases was not reported. Unfortunately, we did not achieve the same therapeutic response in three of our cases after flecainide and digoxin were given for 7, 10, and 5 days, respectively. In one case, digoxin had to be stopped because of side effects in the mother.

We opted to use amiodarone by intraperitoneal injection for a number of reasons. First, amiodarone has been shown to be highly effective in refractory supraventricular tachycardia, even in the presence of foetal hydrops, with low foetal mortality.[12–14] Strasburger et al[14] reported 93% efficacy of transplacental amiodarone when used alone or in combination regimens in foetal supraventricular tachycardia complicated by ventricular dysfunction or hydrops. However, transplacental transfer of amiodarone is known to be limited and foetal concentrations were shown to be 10–12% for amiodarone and 20% for its active metabolite desethylamiodarone.[12] Therefore, in resistant cases, the alternative is to deliver amiodarone directly to the foetus. Second, the long elimination half-life of amiodarone reduces the number of intraperitoneal injections required to maintain therapeutic drug levels in the foetus. In a study of rats, the terminal half-life of amiodarone after a single dose of intraperitoneal amiodarone (100 mg/kg) was 54.7 ± 8.2 hours, whereas after multiple intraperitoneal dosing (50 mg/kg/day 5 days a week) the concentration of amiodarone in plasma was halved within 8.4 days. On the basis of the elimination data, the time to steady state is about 2 weeks. This corresponds to the average time to conversion (11.5 days) with intraperitoneal amiodarone in our series of hydropic foetuses with supraventricular tachycardia.[26] Third, amiodarone has only a minor negative inotropic effect compared with other agents.[27]

One major concern of amiodarone is the potential for causing hypothyroidism in the foetus. Amiodarone contains 37% iodine by weight, and its structure resembles that of thyroxine. Transplacental transfer of amiodarone and desethylamiodarone exposes the foetus to excess iodine, causing persistent inhibition of foetal thyroid function, which may lead to hypothyroidism and goitre.[28,29] Lomenick et al[30] reviewed 69 reported cases of amiodarone use during pregnancy in which the infant's thyroid function was documented. In three cases, amiodarone was given directly via the umbilical vein.

The overall incidence of hypothyroidism was 23%, but all cases of neonatal hypothyroidism were transient. Interestingly, the authors noted that the development of hypothyroidism was neither related to the cumulative amiodarone dose nor duration of amiodarone exposure. Of the seven surviving neonates in our series, transient biochemical hypothyroidism was found in two neonates who required short-term treatment.

Evidence concerning the long-term neurological morbidity of infants exposed to amiodarone in utero is limited. Magree et al compared the neurodevelopment of 10 children exposed to amiodarone in utero to age-matched controls. Amiodarone was prescribed for maternal cardiac disease in conjunction with other drugs. Although the intelligence quotient of the two groups did not differ, the amiodarone-exposed group had poorer expressive language skills compared with the controls.[31] The negative effect on the child's neurodevelopment, however, may be related to other causes such as maternal cardiac disease, concomitant medications, and foetal thyroid insufficiency.

Foetal tachycardia and subsequent hydrops is also a known risk factor for the development of neurological abnormalities. Haemodynamic compromise due to circulatory disturbances and sudden changes in heart rhythm predisposes the foetus to cerebral ischaemia and haemorrhage. The foetus has a narrow autoregulatory range of systemic blood pressure and immature cerebral autoregulation at early gestation, and hence increased susceptibility to cerebral complications.[32,33] Rapid and persistent control of the foetal heart rate is of utmost importance in the prevention of cerebral complications. There were no neurological concerns with any of the children at follow-up and no formal testing of intelligence quotient or language skills was undertaken.

Persistent foetal tachyarrythmias complicated by hydrops fetalis continue to be a challenging entity. Mortality rate in hydrops depends on underlying diagnosis; however, the risk of death is highest for those who were more premature and those who were most ill immediately after birth.[34] Therefore, the risk and benefit of intrauterine therapy versus early delivery of hydropic foetus has to be carefully considered. Intraperitoneal administration of amiodarone is a relatively safe and effective strategy for direct foetal treatment of refractory supraventricular tachycardia associated with hydrops at early gestations when delivery is not appropriate. When transplacental therapy fails to convert these foetuses, the intraperitoneal route is a feasible option, which assures delivery of the drug to the severely hydropic foetus and enables a bolus dose to be delivered for sustained absorption.

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Conflicts of Interest

None.

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