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Acute neonatal arterial occlusion: is thrombolysis safe and effective?

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Abstract

Purpose: We report our experience of the management of arterial occlusion in the newborn.

Methods: A case note review was carried out after ethical approval. Doppler ultrasonography confirmed the occlusion. Thrombolysis was the primary intervention. Surgery was used selectively. A good outcome was one without tissue loss or functional impairment *or* minimal tissue loss without functional impairment. Data are presented as medians with ranges.

Results: Ten patients (9 male; median gestational age, 35.5 weeks [range, 28-39 weeks]) presented on day 1 (range, 1-8 days). Initial management included systemic tissue plasminogen activator (8 patients) and surgery (2 infants in whom thrombolysis was contraindicated). Improvement was noted in 7 of 8 infants treated medically and in both who underwent surgery. Three infants had significant tissue loss. Outcome at 29 months (range, 1.3-95.4 months) was good in the remaining 7.

Conclusions: A multidisciplinary approach, thrombolysis and selective surgery achieved tissue preservation and function in the majority while minimizing complications. Early referral to centers with multidisciplinary teams is recommended.

Thrombo-embolic phenomena are a rare but well-recognized complication of the newborn period. The documented incidence is higher in smaller more premature infants. Three percent of very low and extremely low birth weight infants, admitted to a neonatal unit, had vascular injuries requiring a combination of medical and surgical treatment [1]. Symptoms, signs, and outcomes are dependent on whether the disorder is primarily venous, arterial, or a combination. The experience with venous occlusion in the newborn period is increasing, and recent reports have drawn attention to advances in management [2]. Conversely, there

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is little published data on arterial occlusion in the newborn period and consensus on appropriate interventions and management protocols is still evolving. This reflects, in part, the relative rarity of acute limb-threatening arterial occlusions. We report a series of newborn infants with acute arterial occlusion with a view to highlighting the range of problems encountered, available management strategies, and outcomes.

1. Materials and methods

All infants admitted under the care of a general pediatric surgeon with acute, limb-threatening, arterial ischemia in the 9-year period up to July 2003 were identified. Infants with a corrected gestational age greater than 44 weeks at presentation were excluded. A retrospective case note review of the remainder was undertaken. Evaluation included demographic details, mode of presentation, and clinical and radiologic assessment of extent of ischemia. The time to start treatment (TT) was defined as the time from recognition of vascular occlusion at the local hospital to the commencement of specific treatment based on our unit protocol. Good outcome was defined as no tissue loss or functional impairment or minimal tissue loss with no resulting functional impairment in the affected limb. Details of medical management, surgery, and outcomes were noted.

The initial intervention was massage at the site of arterial occlusion with a view to mechanical clot fragmentation. During the time of this review, our preference was to use medical treatment as a first choice unless contraindicated. This consisted of thrombolysis with tissue plasminogen activator (t-PA) at a dose of 0.25 to 0.5 mg/kg per hour for 6 hours. This was administered with fresh frozen plasma to increase the amount of plasminogen available for the action of t-PA. Unfractionated heparin (15-20 U/kg per hour) was given concurrently and continued for a total of 24 hours to provide low-dose anticoagulation. This combination was repeated if indicated by incomplete resolution of the occlusion based on clinical or Doppler evaluation. In infants with a preexisting intracranial hemorrhage or hemorrhagic tendency, medical treatment was considered to be contraindicated. The initial management of these infants was surgical. Data are reported as median values with ranges.

2. Results

Ten patients (9 male) were identified. The median gestational age was 35.5 weeks (range, 28-39 weeks), and the median age at presentation was 1 day (range, 1-8 days). Six infants had undergone intraarterial cannulation; 5 umbilical artery catheters in the 5 newborns who presented with lower limb ischemia and 1 left brachial artery catheter in 1 infant with ischemia of the left forearm and hand. Three of the 10 infants were born to diabetic mothers and 7 were born by emergency cesarean delivery. Other putative risk factors are outlined in Table 1.

The clinical diagnosis of arterial occlusion was clear in all (Fig. 1). The level of obstruction could be accurately estimated in the majority. The diagnosis was confirmed by Doppler ultrasound in all infants. Early in the series, 2 patients underwent diagnostic angiography and, another, angiography for local delivery of t-PA. This infant developed ischemia of the contralateral leg after the reinsertion of an umbilical artery catheter. This responded to catheter removal and systemic t-PA infusion.

Arterial occlusion sites were varied (Table 1). The TT could be ascertained in 9 infants and ranged from 4 to 48 hours with a median of 21 hours. A thrombophilia screen (antithrombin, protein S and C, plasminogen activity, lupus anticoagulant and anticardiolipin antibodies, *MTHFR* gene mutation, prothrombin gene mutation, factor V Leiden mutation) was performed in all patients before administration

Table 1 Risk factors, interventions, and outcome in newborn infants with acute arterial ischemia

Weight (kg)	Gestational age (wk)	Site of occlusion	Risk factors	Time to starrt treatment (h)	Initial treatment		Outcome
					Medical	Surgery	
4.4	36	Subclavian	Compression	21	✓		Good *
4.6	37	Aorto-Iliac	AC	4		✓	Good
0.8	30	Brachial	AC	27		✓	Good
3.9	39	Femoral	AC	19	✓		BKA
2.2	35	Brachial	PT	31	✓		Good
0.8	30	Popliteal	AC	48	✓		AA
3.8	39	Brachial	–	4	✓		Good
1.3	29	Aorto-Iliac	PT + AC	unknown	✓		Good **
3.8	37	Brachial	–	27	✓		Good
0.9	28	Femoral	AC	12	✓		TKA

AC indicates arterial catheter; PT, polycythemia; BKA, below knee amputation (see Fig. 2); AA, auto-amputation; TKA, through knee amputation.

* Good outcome after release of contractures.

** Good outcome after release of contractures and skin graft.

Fig. 1 Patient number 4—acute arterial ischemia of the right leg.

of fresh frozen plasma. One infant had a transient antithrombin deficiency. The remainder showed no evidence of inherited or acquired thrombophilia.

The initial management was medical in 8 infants according to the previously described protocol. Seven of these showed an improvement in degree and/or extent of tissue ischemia. The other 2 infants had contraindications to thrombolytic therapy (preexisting intracranial hemorrhage) and were treated by left brachial thrombectomy in one and aorto-iliac thrombectomy in the other. Distal blood flow was reestablished in both. Infant number 2 underwent initially successful aorto-iliac thrombectomy but was again noted to have poor lower limb perfusion 48 hours postoperatively. Medical therapy was initiated with an improvement in distal perfusion. However, there was an extension of the preexistent thalamic bleed as a result of which thrombolytic and anticoagulant therapy was discontinued. This child required a ventriculo-peritoneal shunt for hydrocephalus at the age of 1 month, but there were no neurologic deficits on review at the age of 8 years. No other infant had an intracranial hemorrhage on medical therapy. Two infants required fasciotomy for compartment syndrome.

Fig. 2 summarizes the clinical course and outcome of all the infants. Three of the 8 treated medically and both infants treated primarily with surgery had a good outcome after the initial treatment alone. Patient number 8 (Table 1) is the subject of a previous case report [3]. He was a 29-week-

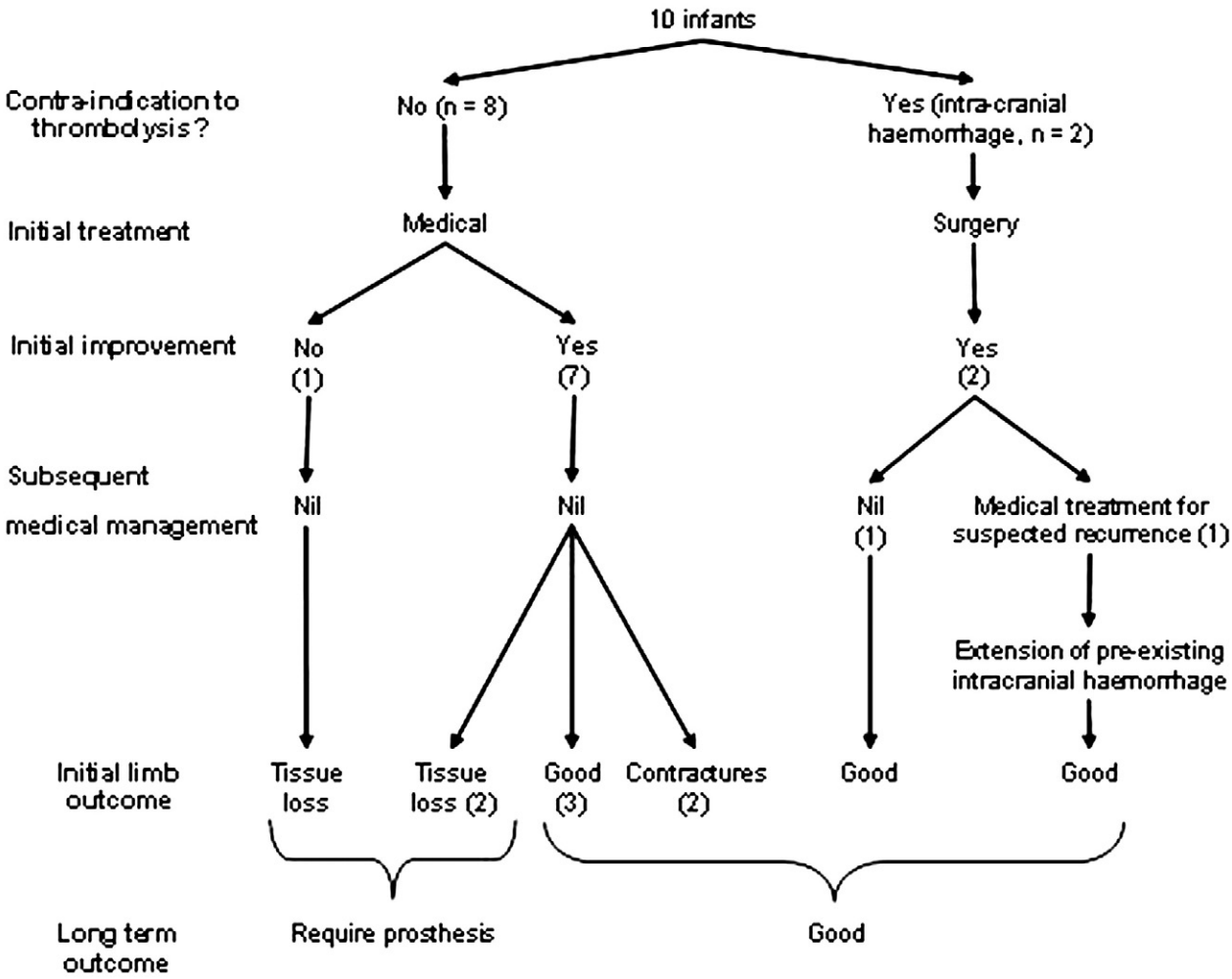

Fig. 2 Flowchart showing clinical course and outcome of infants with arterial occlusion in this series.

gestation twin with bilateral leg ischemia secondary to aorto-iliac occlusion (black leg below the left knee). He responded to tPA and on discharge there was complete resolution of ischemia with residual deformity corrected by subsequent contracture release and skin flap. Follow-up at a year demonstrated left tibial bowing and slight sclerosis of the right tibial metaphysis. Another infant treated medically required release of ischemic contractures then went on to have a good outcome with no functional impairment. At a median follow-up of 29 months (range, 1.3-95.4 months), 3 infants have significant tissue loss secondary to auto-amputation (n = 1) or surgical amputation (n = 2). In this small series, there were no significant differences in TT between those who had tissue or functional loss and those who did not.

3. Discussion

Acute limb-threatening arterial occlusion is a rare neonatal event [4,5]. There is a lack of consensus regarding etiology and management [4,6]. In this series, putative risk factors included an intraarterial catheter (6 infants), sex (9 male), emergency cesarean delivery (7 infants), and maternal diabetes, or very high body mass index (4 mothers). Although iatrogenic vascular injuries have long been recognized as a risk factor for limb ischemia in infants and young children [7], the precise role of other risk factors in the development of arterial occlusion is not known. No persistent hypercoagulopathy was identified in this group of patients.

The initial diagnosis of an arterial occlusion is clinical. We used color Doppler sonography to confirm the diagnosis and site of occlusion. Although angiography remains the theoretical gold standard, in expert hands the detail provided by ultrasonography with Doppler is adequate. It has the further advantages of being noninvasive, readily available, and easily repeatable to monitor treatment. Several case reports and small series describe the use of angiography for imaging and local fibrinolytic delivery [8]. However, arterial access may put a previously uninvolved vessel at risk as was the case in one of our patients. Angiography is no longer part of our routine work-up and we strongly recommend color Doppler sonography for imaging.

A number of guidelines have been published to aid decision making in these infants [9]. Suggested strategies include elevation and warming of the affected limb, application of a glyceryl trinitrate transdermal patch, local papaverine injection around the artery with a bupivacaine nerve block, systemic anticoagulation with heparin, thrombolysis (which may be locally or systemically administered), and surgery. Some recommendations are contentious. For example, in our opinion, an ischemic limb should never be deliberately warmed and elevation does not improve blood flow. In addition, we have encountered a number of infants in our unit with signs of arterial occlusion who have responded rapidly to gentle massage at the presumed site of occlusion. This maneuver appears safe and was not associated with signs of distal embolization. Our practice is to do this at the first sign of arterial insufficiency. Although early referral is of paramount importance, one of the striking aspects of the infants we have managed is the potential for significant "tissue recovery" despite what may initially appear to be established ischemic changes. For example, the patient in Fig. 1 had "gangrene" to the level of the right knee, the extent of which is defined by the area of redness in the illustration. With treatment, this improved to below the knee. He eventually underwent amputation below rather than through the knee which is what had been expected at the time of admission. The explanation for this reversal is unclear but it may be peculiar to young infants and related to better wound healing properties when compared with older children and adults.

The literature related to neonatal arterial occlusion is largely in the form of case reports [10,11], but Friedman et al [12] have one of the larger, single-unit series of newborns with arterial occlusion (n = 5). Two of the infants reported underwent acute thrombolysis [12]. The report highlights areas of controversy related to the administration of thrombolytic therapy to newborn infants and attempts to define the role of surgery in the management of these cases.

Tissue plasminogen activator is a recombinant protein with thrombolytic activity. It exerts its effects by initially binding to clot-bound fibrin. This complex produces plasmin at the site of the clot [13], resulting in dissolution. The use of t-PA in adult practice for the treatment of pulmonary embolism, deep vein thrombosis, and acute myocardial infarction has been extensively reported. However, information regarding its use in childhood and infancy is limited [14] and most reports group arterial and venous thrombosis in a diverse age range together [15]. Regimens in use for children have, in the main, been extrapolated from adult data [16]. Although there is some evidence that it is superior to older thrombolytics in childhood [14], it is significantly more expensive [9] and there have been no prospective randomized studies to date documenting its efficacy. It is unclear whether in the neonatal age group systemic delivery is as effective as local infusion. The exact dosing regime should be tailored to the individual patient and the risk of bleeding weighed up against that of not achieving lysis by the use of a lower dose of t-PA. Outcomes have been favorable in our series although we recognize that major complications have been reported with the use of t-PA in children [17]. Zenz et al [18] attempted to quantify the bleeding risk from a range of different thrombolytic agents. In a series of 929 children who underwent thrombolysis for a variety of reasons, intracerebral bleeding occurred in 1 of 83 term infants compared with 11 of 86 preterm infants. Preterm infants treated in the first week of life had a higher incidence. Given the risk of spontaneous ventricular hemorrhage in prematurity, the additional number specifically attributable to thrombolysis

is difficult to ascertain. Nevertheless, the arguments are compelling and faced with a sick very low birth weight baby in the first week of life a significantly higher threshold for thrombolysis seems appropriate.

With technical advances, vascular surgery in very small infants is less daunting than in the past [19,20] and some authors advocate a low threshold for surgery in the management of acute arterial ischemia in infants [12]. Whether this approach results in the best outcome is unclear. Flanigan et al [7] have evaluated children with a mean age of 31 months (range, 1 day–13 years) and an iatrogenic vascular injury, most of which were caused by cardiac catheterization. Nine percent of those managed with surgery developed leg-length discrepancies compared with 23% of the nonsurgically treated group. This was attributed to prolonged ischemia in the nonsurgical group [7]. Newborn infants, however, represent a distinct group of patients and these results from older children may not be entirely relevant. We believe that thrombolysis with t-PA and adjunctive anticoagulation with heparin should be the initial approach with surgery reserved for those with specific contraindications. The role of surgery in cases that do not have a satisfactory response to medical therapy is less clear, particularly in those who arrive with "established gangrene." Three patients in our series treated medically had a poor outcome with loss of tissue (Fig. 2). Whether surgery at any stage would have improved the outcome is not known, particularly as a clinical improvement was seen in 2 of these infants after initiation of medical treatment. It could be argued that in the one infant who did not have an initial response, early surgical intervention may have salvaged some tissue. It is of interest that a report in which newborns with arterial occlusion were managed primarily with surgery and anticoagulants used sparingly, there was a high incidence of significant long-term sequelae [21]. A more recent report from Melbourne recommending a multidisciplinary approach used a combination of aggressive heparinization augmented by thrombolyis or surgery [22]. Five of 11 patients underwent arteriotomy, embolectomy, and microvascular reconstruction. Three had minor limb tissue loss and 1 child required a skin graft and subsequent scar revision. Another lost terminal digits of 3 fingers. These reports emphasize the fact that each algorithm advocated for this condition is imperfect.

Three aspects of arterial occlusion in the newborn should be emphasized; first, iatrogenic arterial injury is a major contributor (directly implicated in 60% of infants in this series). Reduction of this morbidity may result from judicious use and correct placement of umbilical arterial catheters and the avoidance of femoral and brachial arterial puncture where possible. Second, a team of specialists is required to manage these infants including general pediatric and plastic surgeons with microvascular skills, orthopedic surgeons, and interventional radiologists. The majority of

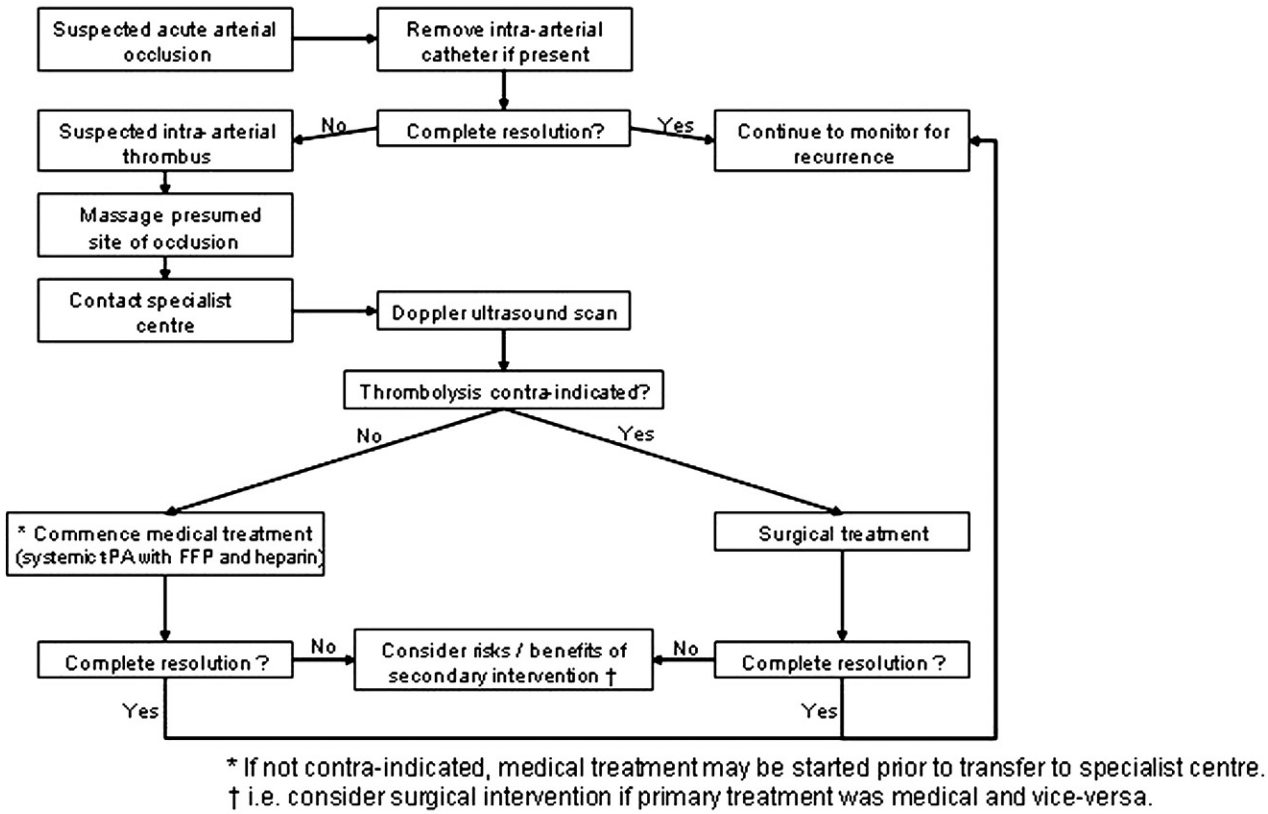

Fig. 3 Flowchart of recommended course of management for acute arterial occlusion.

neonatal units do not have direct access to skilled vascular surgeons with an extensive experience of dealing with small infants. We have evolved a policy of admission under the care of a general pediatric surgeon. There is, however, immediate and full involvement of the neonatal intensivist and pediatric hematologist. Third, it is evident that referral pathways for this condition are often unclear. Limb-threatening delays may result from this uncertainty, and, ideally, a protocol to deal with this clinical emergency should be agreed in each neonatal unit.

Arterial occlusion in the newborn is a rare and challenging condition. We report 10 infants with limb-threatening, acute arterial occlusion managed using combinations of high-dose, short-duration thrombolysis; low-dose heparin; and selective surgery. Our management strategy based on this experience is illustrated in Fig. 3. We found it effective and safe in the majority.

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