



Audit of Acute Limb Ischaemia in a Paediatric Intensive Care Unit

A Dissertation

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1 DECLARATION

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2 CERTIFICATE OF APPROVAL

The undersigned have examined the dissertation entitled ‘**Audit of Acute Limb Ischaemia in a Paediatric Intensive Care Unit**’ submitted by **DR JESSE MUSOKOTA MUMBA**, and hereby certify that it is worthy of acceptance and approve that the above mentioned has fulfilled part of the requirements for the award of the degree of **Master of Medicine in Anaesthesiology** by the University of Cape Town.

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3 ABSTRACT

Objective: Iatrogenic acute limb ischaemia in paediatric patients is a well-recognised complication of vascular access. This retrospective review of a paediatric intensive care unit identified patients who developed iatrogenic acute limb ischaemia between January 2008 and July 2013.

Methods: The medical records of inpatients diagnosed with acute limb ischaemia during the study period were reviewed. Patients with other causes of acute limb ischaemia were excluded. A descriptive analysis of demographics, primary diagnosis, type of vascular access used, affected anatomical region, clinical presentation, type of therapy, type of block, response to intervention used and outcomes was conducted.

Results: A total of 28 patients presented with signs of acute limb ischaemia, of whom 28.6% were aged <30 days, 46.4% were between one and 12 months and 25% were between one and five years old; 78.6% of the affected limbs were lower limbs. Four patients had resolution of ischaemia upon removal of the vascular access devices. 23 patients received various forms of pharmacological sympathectomy, in addition to conservative therapy. One patient had missing data on the type of sympathectomy that was done. The response to the sympathectomies was: 60.9% good, 8.7% moderate, 8.7% poor and in 21.7% no responses. Documented tissue loss related to the ischaemia occurred in six (21.4%) of the 28 patients.

Conclusions: Iatrogenic acute limb ischaemia in children are usually managed without surgical intervention. Pharmacological sympathectomies lead to increased blood flow to the affected limb via vasodilatation of collateral vessels, with an added advantage of

reducing ischemic pain. The improved blood flow is postulated to avoid and/or minimise the amount of tissue loss. Pharmacological sympathectomies may, thus, have a role to play in the management of iatrogenic acute limb ischaemia in the paediatric population.

Keywords and phrases: Paediatric, acute limb ischaemia, complications of arterial cannulation, treatment algorithms, umbilical artery catheter complications.

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5 DEDICATION

I dedicate this dissertation to my lovely wife, Irina Mumba and my two beautiful daughters, Melissa Ngosa Mumba and Michelle Natasha Mumba. Thank you for being there and allowing me time off to work on this dissertation. I love you all very much.

6 ABBREVIATIONS

ALCPA = Anomalous Left Coronary Artery From the Pulmonary Artery

ARDS = Acute Respiratory Distress Syndrome

ASD = Atrial Septal Defect

AVSD = Atrioventricular Septal Defect

IALI = Iatrogenic Acute Limb Ischaemia

MODS = Multiple Organ Dysfunction Syndrome

NEC = Necrotising Enterocolitis

PDA = Patent Ductus Arteriosus

PICU = Paediatric Intensive Care Unit

PS = Pharmacological Sympathectomy

RXH = Red Cross War Memorial Children's Hospital

TAPVD = Total Anomalous Pulmonary Venous Drainage

TOF = Tetralogy of Fallot

VSD = Ventricular Septal Defect

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8 PART A: PROPOSAL

Proposal for an Audit of Acute Limb Ischaemia in a Paediatric Intensive Care Unit

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8.1 Aim of the Audit

Acute limb ischaemia following vessel cannulation is a recognised and well-documented complication in the paediatric population. The management of the acute limb ischaemia in this patient population is aimed at improving blood flow to the affected limb. There are no specific therapies for acute limb ischaemia and published protocols for management of these patients are not inclusive of all the proposed interventions present in the literature.¹⁻

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Our intention is to review the Red Cross War Memorial Children's Hospital paediatric intensive care unit and cardiothoracic databases from January 2008 to July 2013 to identify patients who have developed acute limb ischaemia secondary to cannulation of arteries, veins or both vessels. A review of the clinical notes will be carried out to identify the indication for vascular access and possible causes, as well as management strategies employed to improve blood flow to the affected limbs in these patients. This audit aims to gather general information about the incidence, aetiology, management and outcomes of the problem to assist the planning and formulation of treatment protocols. The outcome of the audit is likely to be used in the planning of a formal prospective audit of acute limb ischaemia in the paediatric intensive care and will form the basis of a master's degree dissertation for Dr Jesse M. Mumba.

8.2 Background

Although uncommon, acute limb ischaemia is a well-recognised complication of arterial and venous cannulation in both adults and children. The incidence of complications related to arterial and venous catheterisation in the general paediatric intensive care unit is similar to that found in the adult intensive care setting.⁸⁻¹¹ The aetiology of acute limb ischaemia is multi-factorial. The pathophysiology of acute limb ischaemia is not well understood, though proposed theories include thrombosis, embolism, vessel spasm following manipulation, vessel transection and perivascular haematomas causing compression of inflow and outflow of blood to the limb.^{3-6, 9, 12} The natural history of acute limb ischaemia related to catheterisation is unknown, but limb infarction necessitating amputation does occasionally occur.¹³ Clinicians faced with an ischaemic limb undertake various therapeutic measures to try to improve the blood flow to avoid limb infarction and the need for amputation.

The management of acute limb ischaemia focuses on improving the perfusion to the affected limb.³ Perfusion pressure is the difference between the arterial and the venous pressures of the affected limb. Therefore management of acute limb ischaemia can be managed by increasing the arterial pressure or reduction of venous pressure or both. Arterial blood flow can be improved by conservative, medical or surgical interventions. Conservative measures consist of removal of the arterial catheter, warming the contralateral limb and elevation of the affected limb. Medical interventions include, decreasing vasoconstrictor doses, use of systemic vasodilators, peri-arterial infiltration of vasodilators, intra-arterial vasodilator injection and anticoagulants. The surgical

interventions include thromboembolectomy, end-to-end microvascular reconstruction and graft bypass surgery. Venous pressure can be reduced by elevating the limb, removing constricting bandaging and removal of venous catheters.^{1, 2, 5-7, 12-14}

The last resort intervention in adults is bypass grafting of the affected area, usually an arterial bypass with an autologous venous graft. In the absence of microsurgical specialties, bypass surgery in children less than 2.5 years old is considered not a practical option.¹⁵ The small diameter of the vessel makes it technically difficult. The rarity of this complication means that non-microvascular surgeons never develop specific technical skills in repair of vessels of this size. There is evidence in literature that graft thrombosis occurs more often in the paediatric population.¹⁵ The high failure rates after surgical intervention in adults is worse in children due to the low flow rates through small vessels, combined with the coagulation changes encountered in a child who is actually ill.^{1, 3, 5, 15}

There are reports of the use of pharmacological sympathectomies using local anaesthetics in both the upper and lower limb ischaemia in both adults and children.^{2, 6, 7, 13, 14, 16, 17}

These reports are mainly case reports or small series studies and relate to cannulation-associated ischaemia as well as ischaemia from other causes. At Red Cross War Memorial Children's Hospital, intensivists refer patients with acute limb ischaemia to the paediatric anaesthetic services for possible pharmacological sympathectomies when conservative management has failed and limb infarction appears to be a possible outcome. How often this occurs, what conservative methods are being used and the regional anaesthesia technique is not known at present.

8.3 Rationale

The incidence, aetiology, management and outcome of acute limb ischaemia in the paediatric intensive care unit at Red Cross War Memorial Children's Hospital have not been established by a formal audit. As such, no clearly defined protocol for assessing or managing these patients exists. Although invasive regional anaesthetic techniques are employed, based on limited literature reports of success, the outcome related to these procedures has not been formally reviewed.

8.4 Methodology

Design and Setting

This is a retrospective audit of clinical databases. This study is to be conducted at a tertiary level paediatric university hospital.

Patient Selection

The Red Cross War Memorial Children's Hospital intensive care unit and cardiothoracic databases will be searched using the international Classification of Diseases 10th Version (ICD-10) coding for the following terms and ICD-10 numbers as shown in Table I.

Table I. ICD-10 Codes to be used in Database Search.

International Classification of Disease 10 (ICD-10) Terminology	ICD-10 Code Number
Arterial thrombosis or embolus	T81.71-T81.72
Other vascular complications	T81.8
Complication of vascular device NOS*	T81.9

*NOS = Not Otherwise Specified.

The inclusion criteria will be children admitted to the paediatric intensive care unit between January 2008 and July 2013 for different illnesses with documented acute limb ischaemia following vessel manipulation.

Data Collection

All data pertaining to the participant will be collected on a standardised form (see Appendix One). The following data will be collected as shown in Table II.

Table II. Data to be Collected from Patients' Folders.

Demographic data	Age, gender, weight
Admission timeline	Date of admission, date of incident
Admitting diagnosis	ICD10 term and code
Associated conditions	Sepsis, shock, coagulopathy, trauma
Associated therapy	Fluids preceding six hours, blood products, inotropes, vasoconstrictors
Details of limb involvement	Anatomical regions, side
Presenting sign	Pallor, decreased perfusion, decreased pulse, decreased temperature, infarcted skin, pain
Aetiological factors	Venous catheter, arterial catheter, venepuncture, arterial puncture, trauma
Conservative management	Warming, limb elevation, catheter removal, systemic vasodilators, decreased vasoconstrictors
Outcome	Resolution, repeat intervention, infarction, amputation

Data Analysis

Descriptive data analysis will be applied; the minimum, maximum, median and 25th, 50th and 75th percentiles for the parameters will be established.

Dissemination of Results of Study

The results of this study are to be presented to the Department of Paediatric Anaesthesia and Surgery, the annual meetings of the Society of Anaesthesiologists of South Africa and the Society of Surgeons of South Africa. The results will also be submitted to a peer-reviewed journal for consideration as a publication. This study in part forms the basis of a MMed thesis by Dr Jesse M. Mumba.

8.5 Ethical Considerations

This study will be compliant with the principles enunciated in the Declaration of Helsinki.¹⁸ The on-going ethical conduct of the trial remains the responsibility of the principle investigator. The principle investigator, Dr Jesse M. Mumba, is a registrar in the Department of Anaesthesia at Groote Schuur Hospital and the University of Cape Town. The primary supervisor, Dr Owen Hodges, and the co-investigator, Prof. J. Thomas, Head of Paediatric Anaesthesia at Red Cross War Memorial Children's Hospital, are holders of a certificate of 'Good Clinical Practice (GCP)', having attended this course.

Permission to Collect Data

Permission to review data from the Red Cross War Memorial Children's Hospital paediatric intensive care unit and cardiothoracic databases will be obtained from the database administrators. Permission to review the clinical records of patients from the database will be obtained from the Red Cross War Memorial Children's Hospital medical superintendent once the Ethics Committee approval for review has been granted.

Protecting Patient Confidentiality

The paediatric intensive care unit and cardiothoracic databases will be reviewed. Patients identified from the database will have their folder number entered onto a spreadsheet. This spreadsheet will be used to retrieve the folder from the hospital records office and to ensure that subsequent admissions or ischaemic events are not recorded to new patients. This record of hospital admission numbers will be maintained to correlate laboratory data with clinical outcomes. Only the principle investigator will have access to the record log and this information will not go outside the University of Cape Town. Each participant will be assigned a unique study number. This is the number that will appear on the data collection sheet. The participants will thus be delinked from their hospital numbers.

Data Storage and Record Safekeeping

The patients' clinical records retrieved from the hospital records office will be reviewed only at Red Cross War Memorial Children's Hospital. They will not leave the hospital site. The hospital record will be returned to the hospital records office at the earliest possible time. Study records that identify the patient will be kept confidential, as required

by law. Privacy regulations providing safeguards for privacy, security and authorised access will be adhered to. Except when required by law, the names, hospital numbers, addresses and telephone numbers or any other direct personal identifier will not identify the patient in the study records.

Data collected will be stored in a secure area in the Department of Anaesthesia at the Red Cross War Memorial Children's Hospital. The data collection sheets and the data collected remains the property of the University of Cape Town.

Informed Consent

We do not intend to seek informed consent from the participants or their families. The de-identification process will allow anonymous data collection. The results will be polled and tabulated, and there will be no discernible information by which any patient will be able to be identified from the data.

No-Fault Insurance

There is no anticipated requirement for no-fault insurance, because this is a retrospective audit.

Risk/Benefit Assessment

This audit does not pose any risk to the participants. Based on the information gathered, a formalised approach to assessing and treating limb ischaemia in the paediatric intensive care unit will be established. Treatment protocol/guidelines will be established to guide management of acute ischaemic limbs in this patient population. In addition, future

researchers will be able to formulate a prospective study of acute limb ischaemia in the paediatric intensive care unit at Red Cross War Memorial Children's Hospital.

Funding

This audit does not require specific funding. The principle investigator will be performing the reviews in his personal and research time as allocated by the University of Cape Town's Department of Anaesthesia.

Disclosure of Financial Interests

There is no financial interest or conflict of interest to declare.

8.6 References

1. Baserga M, Mariana C M, Asha Puri M, Augusto Sola M. The use of topical nitroglycerin ointment to treat peripheral tissue ischemia secondary to arterial line complications in neonates. *J Perinatol* [Internet]. [Cited 2013 Aug 19];22(5):416–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12082481>
2. Lagade MR, Poppers PJ. Stellate ganglion block: a therapeutic modality for arterial insufficiency of the arm in premature infants [Internet]. *Anesthesiology*. 1984. pp. 203–4. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6465603
3. Downey C, Aliu O, Nemir S, Naik-Mathuria B, Hatef DA, Bullocks JM, et al. An algorithmic approach to the management of limb ischemia in infants and young children. *Plast Reconstr Surg* [Internet]. 2013 Mar [cited 2013 Oct 30];131(3):573–81. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23142939>
4. Kayssi A, Shaikh F, Roche-Nagle G, Brandao LR, Williams SA, Rubin BB. Management of acute limb ischemia in the pediatric population. *J Vasc Surg* [Internet]. Society for Vascular Surgery. 2014;60(1):106–10. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0741521414001530>
5. Hobman J, Khandwala A, Batchelor A. Management of iatrogenic lower limb ischaemia in children. *Br J Plast Surg* [Internet]. 2004 Apr [cited 2013 Oct

30];57(3):245–51. Available from:

<http://www.sciencedirect.com/science/article/pii/S0007122603005666>

6. Taub PJ, O’Connell JP, Singh A, Pinto A, Kapklein M, Goltzman C, et al. Acute ischemia of the lower extremity in the pediatric population: a protocol for management. *Mt Sinai J Med*. 2006;73(8):1074–8.
7. Tobias JD. Clinical review: Therapeutic applications of regional anaesthesia in paediatric-aged patients. 2002;(2):0–5.
8. Frezza EE, Mezghebe H. Indications and complications of arterial catheter use in surgical or medical intensive care units: analysis of 4932 patients. *Am Surg*. 1998;64:127–31.
9. King MA, Garrison MM, Vavilala MS, Zimmerman JJ, Rivara FP. Complications associated with arterial catheterization in children. *Pediatr Crit Care Med* [Internet]. 2008;9(4):367–71. Available from:
http://journals.lww.com/pccmjournal/Fulltext/2008/07000/Complications_associated_with_arterial.2.aspx
10. Scheer B, Perel A, Pfeiffer U. Clinical review: Complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine. *Crit Care*. 2002;6(3):199–204.
11. Schindler E, Kowald B, Suess H, Niehaus-Borquez B, Tausch B, Brecher A. Catheterization of the radial or brachial artery in neonates and infants. *Paediatr Anaesth* [Internet]. 2005 Aug [cited 2013 Aug 17];15(8):677–82. Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/16029403>

12. Arshad A, McCarthy MJ. Management of limb ischaemia in the neonate and infant. *Eur J Vasc Endovasc Surg* [Internet]. Elsevier Ltd. 2009 Jul [cited 2014 Jan 1];38(1):61–5. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19362027>
13. Sanchez V, Segedin ER, Moser M, Pallares VS. Role of lumbar sympathectomy in the pediatric intensive care unit. *Anesth Analg* [Internet]. 1988 Aug;67(8):794–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3394971>
14. Hargreaves DM, Spargo PM, Wheeler RA. Caudal blockade in the management of aortic thrombosis following umbilical artery catheterisation. *Anaesthesia* [Internet]. Blackwell Publishing Ltd. 1992 Jun 1;47(6):493–5. Available from: <http://dx.doi.org/10.1111/j.1365-2044.1992.tb02273.x>
15. Lazarides MK, Georgiadis GS, Papas TT, Gardikis S, Maltezos C. Operative and nonoperative management of children aged 13 years or younger with arterial trauma of the extremities. *J Vasc Surg* [Internet]. 2006;43(1):72–6. Available from: <http://www.sciencedirect.com/science/article/pii/S0741521405017039>
16. Breschan C, Kraschl R, Jost R, Marhofer P, Likar R. Axillary brachial plexus block for treatment of severe forearm ischemia after arterial cannulation in an extremely low birth-weight infant. *Pediatr Anesth* [Internet]. Blackwell Publishing Ltd. 2004 Aug 1;14(8):681–4. Available from: <http://dx.doi.org/10.1111/j.1460-9592.2004.01282.x>
17. Avenant C, Kirsten G. Anterior interscalene approach to the brachial plexus using a nerve stimulator as rescue therapy for arterial occlusion due to an indwelling brachial artery cannula in infants. *South African J Reg Anaesth* [Internet]. 9–12.

Available from: http://sajra.co.za/articles/February_01_AnteriorIntersaclene.pdf

18. WMA General Assembly. Declaration of Helsinki. Ethical principles for medical research involving human subjects. J Indian Med Assoc [Internet]. 2013

Jun;107(6):1–8. Available from:

<http://www.wma.net/e/policy/b3.htm> \n <http://www.ncbi.nlm.nih.gov/pubmed/2414>

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9 PART B: LITERATURE REVIEW

9.1 Objectives of the Literature Review

The review commences with an overview of the incidence and pathogenesis of acute limb ischaemia to contextualise the discussion of treatment methods. The next key area of the review is to analyse the literature on treatment methods used in the management of acute ischemic limb in the paediatric population. The review also focuses on what is known about the use of pharmacological sympathectomies – i.e. neuraxial and peripheral nerve blocks – in the treatment of acute ischemic limbs in the paediatric population. Finally, the review focuses on published management protocols for paediatric acute limb ischaemia occurring as a result of iatrogenic vessel manipulation, the evidence that exists to support their use and the place that pharmacological sympathectomies might have in these protocols.

9.1.1 Literature Search Strategy, Inclusion and Exclusion Criteria

- a. The following databases were searched: PubMed, Medline, Science Direct and Google Scholar; and the relevant articles were analysed. The key words and phrases used in the databases search were: paediatrics limb ischaemia, paediatric limb ischaemia, complications of arterial cannulation, treatment algorithms of paediatric acute limb ischaemia, iatrogenic arterial injuries, aetiology of acute limb ischaemia, therapy, limb salvage and micro-vascular surgery, complication of arterial and venous catheterisation, umbilical artery arterial catheter complications and complications related to vascular devices.

- b. A search to analyse the literature on sympathectomies to treat paediatric acute limb ischaemia was performed using the following search terms: regional anaesthetic technique, caudal blockade, peripheral nerve blocks and neuraxial blocks for treatment of ischemic limb or the pain related to acute limb ischaemia, treatment protocols for paediatric patients with an acute ischemic limb and ultrasound guided blocks.

- c. The following exclusion criteria were used: literature referring to the adult population only, ischaemia due to thrombogenic conditions such as vasculitis of various aetiologies and coagulopathies. Non-English articles were also excluded.

9.2 Introduction to the Literature Review

Acute arterial insufficiency is a known complication following venous and arterial access.¹ There are numerous reasons for single puncture or placement of catheters in arteries and veins undertaken in paediatric intensive care units (PICU).²⁻⁶

Venous catheters are commonly placed for administration of hypo and hypertonic solutions, vasoactive drugs and as a mode of venous access when peripheral access is problematic. Arterial catheters are placed to facilitate continuous blood pressure monitoring, especially during surgery with anticipated large fluid shifts, and to manage doses of inotropes or hypotensive drugs, for frequent sampling of blood and for adjustment of ventilator setting as guided by arterial blood gas.⁷

Acute limb ischaemia is a clinical diagnosis based on signs and symptoms of reduced perfusion. These include a reduction in temperature of the affected limb compared to the

unaffected one, reduced capillary refill, mottling of the skin and usually accompanied by ischemic pain. Confirmation of the diagnosis is done by studies such as Doppler and blood vessel ultrasound by demonstrating a reduction in Doppler signal or the presence of an intravascular clot. The gold standard in confirming reduction in perfusion is angiography of the affected limb.^{8,9}

The consequences of limb ischaemia represent a spectra from ischemic pain and skin changes with or without tissue loss to complete loss of limb, systemic sepsis with subsequent multi-organ failure and death.⁷ Early diagnosis and aggressive management have the potential to avoid catastrophic events. Chronic sequelae reported as a result of vascular insufficiency include limb shortening, poorly developed muscles and other deformities of the affected limb.¹⁰⁻¹⁴

9.3 Incidence of Complications Following Blood Vessel Cannulation

The overall incidence of complications as a result of placement of intravascular catheters in the paediatric population is estimated at about 10%. The true incidence of iatrogenic acute limb ischaemia is unknown but the younger the patient the higher the risk.⁷ Apart from acute vascular insufficiency, other common complications are said to be bleeding with or without formation of haematoma, infection at the site of puncture, nerve injuries and thrombus formations with peripheral embolisation.⁷ The risk of accidental arterial puncture during venous cannulation using landmark techniques is quoted at 14%.⁸ The use of ultrasound guidance during vessel cannulation greatly reduces this risk.^{4, 15}

9.4 Pathogenesis of Acute Limb Ischaemia

Pathogenesis of acute ischemic limb following an iatrogenic manipulation is multifactorial.^{2, 5, 12} The interplay between local and systemic factors involved in coagulation cascade determine whether limb ischaemia will occur or not. Limb ischaemia is a result of decreased perfusion distal to the site of injury leading to a mismatch between the oxygen supply versus the demand. The degree of collateralization and the ability to compensate for the decreased perfusion ultimately determines limb survival.^{9, 13, 14, 16, 17}

The perfusion pressure to a limb is the pressure difference between the mean arterial pressure and the mean venous pressure of the limb. Thus, limb ischaemia can be due to a reduction in limb arterial perfusion pressure or due to increased venous pressure from decreased venous return from the limb. Arterial compromise is the most common cause. Venous obstruction leading to decreased oxygenation of a limb occurs less commonly, but has to be included in the differential diagnosis when defining the cause of the compromised oxygen supply to a limb.^{8, 14}

9.4.1 Local Factors

Acute vessel thrombosis is initiated by mechanical damage to the vascular endothelium with subendothelial tissue and collagen exposure to the circulating blood. This exposure of subendothelial tissue brings about the accumulation and activation of platelets on the surface of the indwelling catheter and vessel, with subsequent interaction with the Von Willebrand factor. The result of this interaction is activation and aggregation of platelets to form prothrombotic plugs. The platelets also release vasoactive substances such as

adenosine diphosphate and thromboxane A₂.¹² Thromboxane A₂ is a potent vasoconstrictor and also further activates other platelets. Decreased blood flow distal to the cannula or thrombi may promote further intravascular thrombosis. In addition, the vessel may spasm around the catheter insertion site, with a possibility of complete occlusion if there is insufficient blood flow around the cannula. The end result is tissue ischaemia distal to the cannulation site.^{1, 5, 8, 17}

In addition to thrombosis and spasm of blood vessel, physical obstruction of the artery by the indwelling cannula, compression of artery by perivascular haematoma and vessel transection are among the most cited causes of arterial vascular insufficiency.^{1, 7, 9, 12, 16} The risk of vessel occlusion is increased by disparity between the vessel lumen and diameter of the catheter as well as by multiple attempts at vessel cannulation. Perivascular haematoma may cause reduced limb perfusion pressure by either compression of the artery and decreased distal perfusion pressure and/or reduction of the venous drainage and elevation of venous pressure of the affected limb.^{7, 16}

9.4.2 Systemic Factors

The activation of the coagulation system by the presence of an indwelling catheter or the exposure of the collagen is aggravated by the fact that the critically ill child is affected by conditions associated with hypotension and low flow states, hypovolaemia and hypercoagulable states. Dehydration may cause relative polycythaemia, leading to changes in the rheology of the blood and hyperviscosity.^{1, 2, 12, 16} The use of systemic vasoconstrictors also contributes to the risk of thrombosis by increasing peripheral vasoconstriction.^{7, 12}

9.4.3 Anatomical Consideration

For indwelling arterial lines, the radial and femoral vessels are reported to be the most commonly used in children due to their easy access.^{7,9}

However, if these are not accessible and invasive monitoring is pivotal to the management of the critically ill child, end arteries like the brachial arteries are used. Theoretically, the use of such arteries increases the risk of limb or tissue loss due to the absence of collateral blood vessels.^{16,18}

In premature babies with very small and difficult to access vessels, the umbilical arteries are often cannulated.^{2,3,12,19} Cannulation of the umbilical artery carries with it the risk of thrombotic processes occurring within the descending aorta. Thrombosis of the descending aorta poses a significant risk of tissue loss.¹⁹

The factors mentioned above in the setting of smaller calibre vessels increases the rate and risk of vessel occlusion should vasospasm or thrombosis occur.²

9.5 Specific Management of Paediatric Acute Limb Ischaemia

The most important factor in the outcome of iatrogenic acute limb ischaemia (IALI) is early diagnosis and appropriate intervention.¹⁴ Whatever treatment is applied, the objective is to improve the perfusion distal to the site of the vessel injury.

Factors that determine what treatment modality is applied include the time from onset of ischaemia to its diagnosis, site of ischaemia, amount of threatened tissue, severity of ischaemia, patient age, size of the affected vessel, and the availability of technical expertise for such procedures as nerve block and microvascular surgery.^{7,9,16,18}

Various treatment modalities have been suggested in the literature. These range from conservative to medical and surgical management. The conservative measures include the removal of the catheter, limb elevation and warming of the contralateral limb (based on reflex vasodilatation of the ischaemic limb). Medical therapy involves the use of vasodilators such as topical 2% nitroglycerine ointment² and intra-vessel papaverine, systemic anticoagulation, thrombolytic agents and changes in vasoconstrictor doses where applicable.^{9, 13, 14, 16} Surgical management with microsurgical techniques include graft bypass and thrombectomies.^{9, 12-14, 16} Pharmacological sympathectomies in the form of peripheral nerve blocks or regional anaesthesia have been used with success, but do not necessarily fall under any of the three arms of therapy mentioned above.^{1, 3, 19-21}

9.5.1 Topical Vasodilator Therapy

In a report of three cases, Baserga et al used topical 2% nitroglycerine to reverse peripheral tissue ischaemia that did not respond to conventional management. The rationale is that vasodilatation of the collateral circulation improves blood circulation to the ischaemic limb. Exogenous Nitroglycerin mimics the effects of endogenous nitric oxide, which is a potent vasodilator, acting via the activation of the enzyme guanylate cyclase, which leads to production of cyclic guanosine monophosphate. Increase in intracellular cyclic guanosine monophosphate leads to relaxation of the smooth muscle of blood vessels, resulting in vasodilatation. The author argues that this is a very safe treatment modality, stating that should side effects develop, such as venous pooling of blood, reduced cardiac output and hypotension, the excess drug can be wiped off. Thus, the author suggests that, provided continuous monitoring of vital signs is available, the

use of 2% topical nitroglycerine offers advantages over drugs administered intravenously.²

9.5.2 Medical versus Surgical Management

Lazarides et al report of a decade's experience in treatment of acute limb ischaemia in preschool children. Mechanisms of injury recorded were penetrating lesions in eight children, blunt trauma in seven children, shotgun in two children and six iatrogenic injuries. Of the iatrogenic injuries, three were as a result of arterial catheterisation. Diagnosis of acute limb ischaemia was arrived at using clinical observation, Doppler ultrasound and angiography. Four patients had angiography done to ascertain the extent of collateral flow. The surgical and medical groups formed the two arms of managing these patients. In the medical arm all patients received 100 units/kg bolus of heparin with subsequent infusions at 20–25 units/kg per hour. The presence of definite threatened limb, false aneurysms and arteriovenous fistulae warranted surgical repair. During the study period, it was found that children less than two and a half years of age did not do well post-surgical intervention. Subsequently, all patients who were under two and a half years or weighed less than 12.5 kilograms were only managed medically.¹³

Hobman reports of a case series of iatrogenic vessel injury in 31 patients treated by six different vascular surgeons. The age ranged from one day old to 25 years of age. Surgical procedures included thrombectomy, embolectomy, arteriotomy, resection and end-to-end repair. Prior to surgical intervention, patients had Doppler ultrasounds done to confirm the presence of a thrombus or disrupted blood flow. A good outcome was said to be the presence of palpable pulses in the immediate postoperative period. The author states that

in the very young, especially the ones under one year old, even after what was considered as technically excellent surgery, the rate of early postoperative thrombosis was high. The theorised explanation for lack of tissue loss despite the recurrences of thrombus formation in the repaired vessel was a well-functioning collateral circulation in the paediatric population. The collateral circulation is thought to compensate for the decreased flow in the main vessels. The absence of atherosclerotic changes in this patient population increases the number of recruitable blood vessels.¹²

Of note is that there is no consensus on the timing of surgical intervention. Downey et al waited for six to eight hours for patients in the conservative arm of treatment before surgical intervention.¹⁴ This is because it is believed that the most frequent cause of ischaemia in the very young is vessel spasm.¹⁴ Friedman suggests that, if the vessel spasm does not resolve to allow for clinical improvement of the limb by the eighth hour, surgical intervention should be undertaken. In Downey's report, Shaker argues that the decision to operate should be undertaken within six hours, while Salerno and Stavorovsky made the decision based on development of abnormal motor signs such as peroneal nerve palsy.^{5, 14}

9.5.3 Management of Iatrogenic Acute Limb Ischaemia with Pharmacological Sympathectomies

In the majority of iatrogenic cases, the ischaemia is a result of vasospasm or thrombus formation in the injured vessel. The duration of the vasospasm following manipulation is four to six hours.^{5, 17} Reduced flow and the presence of a foreign body – i.e. catheters and cannulae – predispose to the formation of clots and may result in partial or complete occlusion of the vessel.¹² Pharmacological sympathectomies (PS) abolish the vasospasm

and any sympathetic nervous system mediated vasoconstriction. The net effect from PS is vasodilatation, opening up of collateral blood vessels and analgesia.⁸

In 1984, Lagade et al first described the treatment of acute limb ischaemia using PS. Lagade used a stellate ganglion block to treat arterial insufficiency in a 1,600-gram premature infant of a 32 weeks' gestation twin pregnancy. In this report, the correct placement of the block was confirmed by the development of ipsilateral ptosis, vasodilatation in ipsilateral upper limb, an increase in the skin temperature and pulse amplitude on ultrasonic Doppler monitor. No tissue loss was documented. He argues that, although no one could predict what the outcome would have been without this intervention, the use of stellate ganglion blockade is useful in the treatment of arterial insufficiency of the upper extremity in very small patients.²⁰

Four years later, Sanchez et al published case series of four patients on the role of lumbar sympathectomy in the paediatric intensive care unit. Sanchez argues that surgical bypass as employed in the adult population is not a practical procedure in the neonate and infant population for reasons as earlier discussed. A 0.25% bupivacaine solution was used in the lumbar sympathectomies. In all four cases, skin temperatures of the toes and dorsal aspect of the feet were monitored. They also employed ultrasonic Doppler to monitor flow in the dorsal pedalis, posterior tibial and femoral arteries. In one of the four cases, a continuous lumbar sympathetic block was used by placement of an 18-gauge catheter for intermittent administration of the local anaesthetic. The outcomes in the cases described were favourable, with no tissue loss in three of four of the cases. The documented tissue loss was reported as a single digit amputation.¹

In preterm babies where vascular access is a challenge, the umbilical arteries are catheterised for the purpose of monitoring and blood sampling. This type of vascular access is only undertaken when the benefits of having an arterial line outweigh the associated risks. The most severe complication is aortic thrombosis, which carries a high morbidity and mortality rate. Due to the size of the preterm babies, the option of surgical thrombectomy presented a big challenge for the vascular surgeons. Hargreaves et al were the first ones to describe the use of caudal block to treat thrombosis in the aorta secondary to umbilical artery catheterisation. The report involved a preterm baby weighing 1.3 kg delivered at 29 weeks' gestation. Acute limb ischaemia secondary to aortic thrombosis was confirmed on Doppler studies. The infant was also found to have a Grade 1 intraventricular haemorrhage thus use of anticoagulants or thrombolytics was contraindicated. The umbilical catheter was removed, but no improvements were noted on conservative therapy with morphine, intravenous fluids and antibiotics. A single shot caudal block was performed, which lasted for six hours. Its effects were reported to be reduction in the heart rate from 200 to 160 beats per minute, a respiratory rate drop from 90 to 60 breaths per minute and less distress in handling the ischemic region of the body. A paediatric extradural catheter was placed for continuous caudal blockade. A 0.25% solution of bupivacaine was infused at 0.1-0.2 ml per hour to achieve the desired analgesic effects. A bone scan done on follow-up showed infarction of femoral epiphyses. Tissue loss was reported as loss of the fifth digit on the right foot. Despite suspicion of spinal cord infarction due to absence of spontaneous movements, spontaneous movements in both limbs reappeared eight weeks later. The infant had a neurogenic bladder requiring intermittent catheterisation. The author argues that preterm

neonates feel pain, respond to painful stimuli and exhibit the stress response. The stress response leads to an increase in the levels of stress hormones such as catecholamine, cortisol and antidiuretic hormones. These hormones are responsible for the pathophysiological changes noted, such as a tachycardia, vasoconstriction, hyperglycaemia, increased metabolic rate and water retention. The use of caudal blockade had a dual effect of vasodilatation and blunting of the deleterious effects of the stress response.¹⁹

Avenant et al described the use of anterior interscalene approach to the brachial plexus using a nerve stimulator as a rescue therapy for arterial occlusion due to an indwelling brachial artery cannula in seven infants. The demographics of these patients were infants with birth weights ranging from 750 to 3800 grams, gestation ages between 28 and 40 weeks and one four-month-old infant. Difficulty in arterial cannulation in these infants led to use of end arteries such as the brachial artery for the purpose of monitoring of the arterial blood gases and drawing of routine samples of blood. The author reports that, in two of the seven cases, peripheral vasospasm was not abolished post-blockade. This was attributed to the fact that a lesser dose of 1 mg/kg was used compare to the 2 mg/kg used in the other five cases. Even with a high dose, there were no local anaesthetic side effects noted.²¹

In a case report of a 650-gram baby prematurely born at 24 weeks via Caesarean section, Breschan used an axillary brachial plexus block as a rescue therapy to improve blood flow to the compromised upper limb following ulna artery cannulation. He agrees with other authors that no other possible treatment modalities would be suitable for such a small patient. The size of the patient would make surgical intervention technically

impossible. Tissue loss reported was necrosis of the second to the fifth fingers as well as the distal part of the thumb. The tissue loss was attributed to the fact that the patient's size posed a challenge in doing a proper landmark brachial plexus block due to poor pulses, and a nerve stimulator was not used. He also suggests that a continuous block by placement of a catheter would have been of value, except that no appropriate size of catheter was available for such a small patient.³

9.5.4 Complications Associated with Pharmacological Sympathectomies

Pharmacological sympathectomies are not without complications.²² The size of the paediatric patient in most cases makes the use of this type of intervention a challenge. The low blood flow and consequent weak pulsations of arteries in the neurovascular bundle complicate the landmark technique of performing the blocks.³ Other researchers have expressed concern regarding the use of nerve stimulators in the preterm and very low birth weight infants. Complications associated with PS cited in literature are related to the side effects of the local anaesthetics and injury to the neurovascular bundle.^{6, 21, 22} Local anaesthetics cause peripheral vasodilatation by abolishment of the sympathetic innervation to the peripheral blood vessels. The net effect is reduction in peripheral vascular resistance and a drop in blood pressure. The vasodilatation causes the pooling of blood in the lower extremities and a subsequent drop in the venous return. This further negatively affects the cardiac output. If accidental intra-arterial or intravenous administration was to occur, bupivacaine, a local anaesthetic of choice for these blocks, is a potent myocardial depressant. Central nervous system effects range from circumoral paraesthesia, confusion, seizures and coma.²² The injuries to the neurovascular bundle include accidental puncture of the vessels leading to vasospasm and laceration of the

vessels with formation of haematomas. Caudal blocks with placement of catheters are notorious for infection due to the proximity to the perineum. For this reason, some of the authors recommend the removal of catheters at the earliest possible chance.^{1, 4, 6, 7, 19, 20, 23}

9.6 Protocolised Management of Acute Limb Ischaemia in the Paediatric Population

From the reviewed literature, it is evident that the most prominent proposed protocols include heparinisation, thrombolysis and surgical management of acute limb ischaemia. It is important to note that these protocols were written for management of acute limb ischaemia of different aetiologies. There are currently no protocols specifically addressing iatrogenic acute limb ischaemia. The details of each protocol are discussed below.

Coombs et al proposes a multidisciplinary approach to the management of an acute limb ischaemia. Upon diagnosis, the removal of any indwelling vascular access device and a meeting between the plastic/vascular surgeon and haematologist to plan further management is recommended. In this protocol, systemic heparinisation is undertaken if clinical signs of ischemic limb are noted. Thereafter, patients are placed into two categories: absolute and relative operative management. In the absolute operative arm, complete limb ischaemia, pregangrenous changes, paralysis of the limb for more than 24 hours, and Doppler/angiogram showing obstruction with no distal flow for more than 24 hours are indications for appropriate surgical intervention. Post-operatively, the patients are heparinised for another seven to 10 days. In the relative operative arm, capillary refill of more than eight seconds for more than 24 hours, absence of S_pO_2 pulse, damped

Doppler wave and tight compartment are the indications for systemic heparinisation and the use of tissue plasminogen activator. If no clinical improvement is noticed in the four hours post initiation of the above-mentioned treatment, these patients cross over into the absolute operative arm.¹⁶ In this protocol, there is no place for pharmacological sympathectomy using peripheral nerve blocks or neuraxial techniques.

Taub et al also propose a treatment algorithm composed of operative and conservative arms. In this protocol, clinical examination of the site of cannulation, temperature of the affected limb, capillary refill and hand-held Doppler studies are done to differentiate between patients who will require conservative management and those who will need surgical management. Yet again, the decision to operate was based on clear evidence of intimal damage or external compression of the vessel from haematoma. Although PS are included in this protocol, they are considered only at the very end of the management options.⁸

Downey et al used an algorithm with well-defined time frames for crossover from conservative to operative management of ischemic limbs in the paediatric population. The protocol involved children less than five years of age who were referred to the division of plastics and reconstruction surgery. Physical examination of the limb, coupled with Doppler studies, differentiated between patients being put in the conservative or operative arm of treatment. In this protocol, patients with suspected arterial spasm were managed with limb elevation and warming, followed by clinical examination and Doppler imaging six to eight hours later. Patients who showed no improvement crossed over to the operative arm. The decision to operatively manage a patient was based on clear demonstration of complete arterial occlusion.¹⁴

Arshad et al's protocol reports that the use of anticoagulants and/or thrombolytic is not without risks. Contraindications to the use of such therapy include patients at high risks of bleeding, such as a history of recent cardiovascular surgery, and those with a diagnosis of intraventricular haemorrhage and heparin-induced thrombocytopenia. However, he agrees with other authors that surgical thromboembolectomy is a useful technique in older children or in neonates with large vessel thrombosis. Where surgical intervention is undertaken, the author emphasises the need to use autologous veins where possible, giving consideration to the anastomotic technique employed to allow for graft growth as the patient grows.⁴

Georgiadis' and Lazarides' protocol is the most inclusive of treatment modalities available in the literature. This protocol is only recommended for patients three years old or younger. The patients are grouped into four categories: irreversible ischaemia, obvious extremity arterial trauma with non-ischemic limb, obvious extremity arterial trauma with threatened limb, and borderline non-threatened limb. The first two categories warrant surgical management, with caution to wait for demarcation to occur in the absence of septic limb for patients in the first category. In the third and fourth categories, patients receive conservative and medical management, which includes removal of catheter, limb elevation, warming of the limb, thrombolysis with tissue plasminogen activators and heparinisation. In this group, a thought is given to the use of topical nitroglycerine and sympathetic block if patients are very small in terms of body weight. Serial clinical and Doppler examinations are recommended. Patients who show no improvement fall into the operative arms of the protocol.²⁴ The downside to this protocol is that there are no specific time frames of when a patient should qualify to cross over to more aggressive

management.

9.7 Controversies in the Management of Paediatric Acute Limb Ischaemia

The proponents of surgical intervention argue that it is a definitive treatment modality, especially where partial or complete disruption of the vessel is evident. The long-term consequences of not repairing blood vessels such as limb discrepancy are also often cited.^{5, 8, 9, 13, 14} However, the recommendations of these authors cannot be generalised, as their case studies did not include all forms of arterial and venous insufficiencies by locality and mechanism of injury. In one study, despite uneventful surgical repair, the restoration of distal pulses occurred in 48% of patients.¹³ The rest of the patients only regained their distal pulses days to months post-operatively. This implies that the limb viability depends on the degree of collateral blood vessels. Angiogenesis or recanalisation, as clot resolution takes place, may explain the restoration of distal pulses over time.^{4, 8, 12, 24}

Although surgical approaches improve limb perfusion, surgery has other attendant risks: transfer of a critically ill child to theatre,²⁵ instrumentation of the endothelium in the setting of hypercoagulability and the technical difficulty of working with small vessels.^{9, 17, 26} The decision to proceed to theatre has to be driven by evidence of a clearly threatened limb or complete vessel occlusion and availability of specialist in microsurgery.¹³

The proponents of medical treatment for iatrogenic acute limb ischaemia argue that, where partial flow is present, but surgical intervention is technically challenging, the use of systemic anticoagulants, thrombolytics and other vasodilating therapies such as topical

nitroglycerine, intra-vessel papaverine and sympathectomies should be considered.^{2, 4, 13, 16} These authors suggest that, given the high rate of failure of revascularisation procedures in children, the risks of surgery and anaesthesia in the critically ill child are not justified.^{13, 17}

Anticoagulation of patients forms the backbone of the medical management in most of the protocols.^{8, 9, 13, 14} Even though widely used, the CHEST guidelines on antithrombotic therapy in neonates and children suggest that the evidence for use of anticoagulants in this age group is weak.²⁷ The authors of these guidelines recommend that, to employ this treatment modality, a multi-disciplinary body consisting of paediatrician/intensivist, paediatric haematologist or adult haematologist experienced in paediatric haematology must be available, among other staff.^{9, 16, 17} Contraindications to antithrombotic therapy include post-major surgery, coagulopathies, heparin-induced thrombocytopenia and various degrees of intraventricular haemorrhage.^{15, 17}

9.8 Argument for Use of Pharmacological Sympathectomies in the Treatment of Acute Limb Ischaemia

The use of pharmacological sympathectomies (PS) using local anaesthetics is a treatment modality that can bridge the surgical and medical management of patients with iatrogenic acute limb ischaemia in the paediatric population. Children have good collateral circulation and the absence of vascular diseases, such as atherosclerosis, means they are able to mount a good vasodilatory response compared to the adult population.^{1, 9, 19, 20}

PS provide a selective vasodilatation of an isolated limb region. This selective vasodilatation can be useful in the setting where systemic vasoconstrictors are required,

such as in the critically ill child.¹⁵ With the advent use of ultrasound, PS can be achieved with minimal risk of repeated injury of the affected blood vessel. The sympathectomy can be performed in the ICU at the bedside.²⁸

The duration of action of PS ranges from four to 18 hours on average. Friedman states that arterial vessel spasms following an iatrogenic intervention last about four to six hours.⁵ In the majority of iatrogenic acute limb ischaemia, the pathogenesis is that of vasospasm and incomplete blood vessel occlusion,^{2, 3, 21} so it makes physiological sense to use vasodilation therapy in the form of PS as part of the first-line treatment. Depending on the type of block used, the vasodilatation usually exceeds the duration of vessel spasm.^{19, 29}

PS can be used to differentiate between a patient who would require medical or surgical management, but cannot undergo angiography or Doppler studies for various reasons, including non-availability. Although an angiogram is the gold standard investigation for confirming arterial occlusion or vessel disruption in a child with an acute limb ischaemia,^{4, 13, 14} it is not always feasible to perform in a critically ill patient. Apart from the risk involved in the management of critically ill children, angiography poses an added risk of further vessel cannulation and contrast-induced kidney injury.¹² In this setting, Doppler studies are advocated. In the absence of these investigative tools or inconclusive results, a correctly performed PS that does not achieve any improvement in limb perfusion through vasodilatation of collaterals would imply that the risk of potential tissue loss is high. Such a patient may need more aggressive therapy, such as thrombolysis, thrombectomies, surgical reconstruction or graft bypass.^{4, 5, 8, 11, 12, 19, 20}

Another advantage of the use of sympathectomies is reduction of the stress response and pain as a result of ischaemia.¹⁹ The stress response and pain are thought to worsen tissue perfusion by increasing the peripheral vascular resistance through adrenergic mediated vasoconstriction. The adrenergic vasoconstriction is abolished by a PS, with subsequent improvement in blood flow by a factor of six on Doppler studies.^{1, 21}

Regional and peripheral nerve blocks are relatively simple to perform and require less resources than medical and surgical interventions.³⁰ The complications associated with their use can be minimised, especially with the advent use of portable ultrasound machines.²⁸ With the evidence present in the literature, and the ease and promptness with which sympathectomies can be performed, the use of PS should be considered early on in the management of the paediatric iatrogenic acute limb ischaemia.^{3, 4, 6, 19, 21}

9.9 Conclusion

The published protocols for the management of paediatric acute limb ischaemia accord no place or only a limited place for the role of sympathectomies.^{8, 9, 12-14} The benefits of sympathectomies are not limited to the improvement of collateral blood flow, but also include the abolishment of the ischemic pain.¹⁹ The improved blood flow has the ability to minimise or prevent tissue loss altogether.^{1, 20} As soon as an ischemic limb is identified and clinical signs are documented, PS should be employed while multidisciplinary meetings and consultations are convened to plan the subsequent management strategies. Should improved blood flow to an affected limb occur with the sympathetic block, other management elements might not be necessary.^{1, 3, 4, 6, 7, 11, 14, 19, 23}

9.10 Contributions this Study Will Add to the Existing Body of Knowledge

- a. The review allowed us to critically appraise whether, based on pathophysiology and review of current literature, PS have a theoretical role to play in the management of iatrogenic acute limb ischaemia (IALI).
- b. The review allowed us to assess the depth and quality of case reports and series that suggest that sympathectomies can be effective in the treatment of IALI
- c. The review allowed us to critically assess the indications and place of sympathectomies in protocols for management of IALI.
- d. Current clinical practice at Red Cross War Memorial Children's Hospital of use of sympathectomies in the management of IALI is supported in the literature. This study will allow us the opportunity to audit our clinical practice.

9.11 Gaps Identified by the Literature Review

- a. The role of sympathectomies in other forms of acute limb ischaemia has not been clearly defined.
- b. In the published literature, the grading of tissue loss is not standardised. The non-availability of a recognised grading system of tissue loss makes it difficult to compare outcomes from various case reports and series.

- c. There is a need to adopt criteria for what can be considered a resolution of signs of ischaemia. The degree of rise in the temperature of the affected limb and Doppler studies may be good markers.
- d. Current protocols are not specific for management of IALI. Many of the general protocols on management of acute limb ischaemia in the paediatric population do not have well-defined time frames to indicate when to escalate from one treatment modality to the other in a stepwise manner. These protocols are also not inclusive of all outlined management strategies in the literature that have been shown to work.

9.12 References

1. Sanchez V, Segedin ER, Moser M, Pallares VS. Role of lumbar sympathectomy in the pediatric intensive care unit. *Anesth Analg* [Internet]. 1988 Aug;67(8):794–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3394971>
2. Baserga M, Mariana C M, Asha Puri M, Augusto Sola M. The use of topical nitroglycerin ointment to treat peripheral tissue ischemia secondary to arterial line complications in neonates. *J Perinatol* [Internet]. [cited 2013 Aug 19];22(5):416–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12082481>
3. Breschan C, Kraschl R, Jost R, Marhofer P, Likar R. Axillary brachial plexus block for treatment of severe forearm ischemia after arterial cannulation in an extremely low birth-weight infant. *Pediatr Anesth* [Internet]. Blackwell Publishing Ltd; 2004 Aug 1;14(8):681–4. Available from: <http://dx.doi.org/10.1111/j.1460-9592.2004.01282.x>

4. Arshad a, McCarthy MJ. Management of limb ischaemia in the neonate and infant. *Eur J Vasc Endovasc Surg* [Internet]. Elsevier Ltd; 2009 Jul [cited 2014 Jan 1];38(1):61–5. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19362027>
5. Friedman J, Fabre J, Netscher D, Jaksic T. Treatment of acute neonatal vascular injuries-the utility of multiple interventions. *J Pediatr Surg* 1999;34:940–945.
6. Tobias JD. Clinical review Therapeutic applications of regional anaesthesia in paediatric-aged patients. *Pediatr Anesth* [Internet]. Blackwell Science Ltd.; 2002;12(2):0–5. Available from: <http://dx.doi.org/10.1046/j.1460-9592.2002.00773.x>
7. King MA, Garrison MM, Vavilala MS, Zimmerman JJ, Rivara FP. Complications associated with arterial catheterization in children. *Pediatr Crit Care Med* [Internet]. 2008;9(4):367–71. Available from: http://journals.lww.com/pccmjournal/Fulltext/2008/07000/Complications_associated_with_arterial.2.aspx
8. Taub PJ, O’Connell JP, Singh A, Pinto A, Kapklein M, Goltzman C, et al. Acute ischemia of the lower extremity in the pediatric population: a protocol for management. *Mt Sinai J Med*. 2006;73(8):1074–8.
9. Kayssi A, Shaikh F, Roche-Nagle G, Brandao LR, Williams SA, Rubin BB. Management of acute limb ischemia in the pediatric population. *J Vasc Surg* [Internet]. Society for Vascular Surgery; 2014;60(1):106–10. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0741521414001530>

10. Sanchez V, Segedin ER, Moser M, Pallares VS. Role of lumbar sympathectomy in the pediatric intensive care unit. *Anesth Analg* [Internet]. 1988 Aug;67(8):794–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3394971>
11. Troutman R, Feliciano P, Menashe V, Sunderland C, Porter JM. Late complications after femoral artery catheterization in children less than five years of age. *J Vasc Surg* [Internet]. 1990;11(2):297–306. Available from: <http://www.sciencedirect.com/science/article/pii/074152149090273D>
12. Hobman J, Khandwala A, Batchelor A. Management of iatrogenic lower limb ischaemia in children. *Br J Plast Surg* [Internet]. 2004 Apr [cited 2013 Oct 30];57(3):245–51. Available from: <http://www.sciencedirect.com/science/article/pii/S0007122603005666>
13. Lazarides MK, Georgiadis GS, Papas TT, Gardikis S, Maltezos C. Operative and nonoperative management of children aged 13 years or younger with arterial trauma of the extremities. *J Vasc Surg* [Internet]. 2006;43(1):72–6. Available from: <http://www.sciencedirect.com/science/article/pii/S0741521405017039>
14. Downey C, Aliu O, Nemir S, Naik-Mathuria B, Hatef DA, Bullocks JM, et al. An algorithmic approach to the management of limb ischemia in infants and young children. *Plast Reconstr Surg* [Internet]. 2013 Mar [cited 2013 Oct 30];131(3):573–81. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23142939>
15. Benkhadra M, Collignon M, Fournel I, Oeuvarard C, Rollin P, Perrin M, et al. Ultrasound guidance allows faster peripheral IV cannulation in children under 3 years of age with difficult venous access: A prospective randomized study. *Paediatr*

- Anaesth. 2012;22(2):449–54.
16. Coombs CJ, Richardson PW, Dowling GJ, Johnstone BR, Monagle P. Brachial artery thrombosis in infants: an algorithm for limb salvage. *Plast Reconstr Surg* [Internet]. Lippincott Williams & Wilkins; 2006 [cited 2013 Nov 10];117(5):1481–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16641716>
 17. Flanigan DP, Keifer TJ, Schuler JJ, Ryan TJ, Castronuovo JJ. Experience with iatrogenic pediatric vascular injuries. Incidence, etiology, management, and results. *Ann Surg*. 1983;198(4):430–42.
 18. Likar R. Case report Axillary brachial plexus block for treatment of severe forearm ischemia after arterial cannulation in an extremely low birth-weight infant. *Pediatr Anesth*. Blackwell Publishing Ltd; 2004 Aug 1;14(8):681–4.
 19. Hargreaves DM, Spargo PM, Wheeler RA. Caudal blockade in the management of aortic thrombosis following umbilical artery catheterisation. *Anaesthesia* [Internet]. Blackwell Publishing Ltd. 1992 Jun 1;47(6):493–5. Available from: <http://dx.doi.org/10.1111/j.1365-2044.1992.tb02273.x>
 20. Lagade MR, Poppers PJ. Stellate ganglion block: a therapeutic modality for arterial insufficiency of the arm in premature infants [Internet]. *Anesthesiology*. 1984. p. 203–4. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=6465603
 21. Avenant C, Kirsten G. Anterior Interscalene Approach To the Brachial Plexus Using a Nerve Stimulator As Rescue Therapy for Arterial Occlusion Due To an Indwelling

- Brachial Artery Cannula in Infants . South African J Reg Anaesth [Internet]. :9–12.
Available from: http://sajra.co.za/articles/February_01_AnteriorIntersaclene.pdf
22. Jeng CL, Torrillo TM, Rosenblatt MA. Complications of peripheral nerve blocks. Br J Anaesth. 2010;105(Suppl 1):i97–i107.
23. Shah, N., & Lalwani, K. (2003). Continuous Caudal Block : Role in Paediatrics. Indian Journal of Anaesthesia, 47(February), 120–121.
24. Georgiadis GS, Lazarides MK. Comment on “Management of limb ischaemia in the neonate and infant” (Eur J Vasc Endovasc Surg 2009;38:61-65). A proposed algorithm for optimal results. Eur J Vasc Endovasc Surg [Internet]. 2009;38(4):531–2. Available from:
<http://www.sciencedirect.com/science/article/pii/S1078588409003360>
25. Hawkins KC: Transfer of the critically ill child. Br J Anaesth 2002; 2: 170-173.
26. Matos JM, Fajardo A, Dalsing MC, Motaganahalli R, Akingba G a., Murphy MP. Evidence for nonoperative management of acute limb ischemia in infants. J Vasc Surg [Internet]. Elsevier Inc.; 2012;55(4):1156–9. Available from:
<http://www.ncbi.nlm.nih.gov/pubmed/22133454>
27. Monagle P, Chan AKC, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Göttl U, et al. Antithrombotic Therapy in Neonates and Children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest [Internet]. American College of Chest Physicians; 2012 Feb 23;141(2 Suppl):e737S – e801S. Available from:
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278066/>

28. Delvi MB. Ultrasound-guided peripheral and truncal blocks in pediatric patients. Saudi J Anaesth [Internet]. India: Medknow Publications; 2011;5(2):208–16. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3139317/>
29. Shah RD, Suresh S. Applications of regional anaesthesia in paediatrics. Br J Anaesth. 2013;111(Suppl 1):i114–24
30. Macario A. What does one minute of operating room time cost? J Clin Anesth [Internet]. 2010 Jun;22(4):233–6. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0952818010000917>

10 PART C: PUBLICATION-READY MANUSCRIPT

10.1 TITLE PAGE

Audit of Acute Limb Ischaemia in a Paediatric Intensive Care Unit

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10.2 ABSTRACT

Objective: Iatrogenic acute limb ischaemia in paediatric patients is a well-recognised complication of vascular access. This retrospective review of a paediatric intensive care unit identified patients who developed iatrogenic acute limb ischaemia between January 2008 and July 2013.

Methods: The medical records of inpatients diagnosed with acute limb ischaemia during the study period were reviewed. Patients with other causes of acute limb ischaemia were excluded. A descriptive analysis of demographics, primary diagnosis, type of vascular access used, affected anatomical region, clinical presentation, type of therapy, type of block, response to intervention used and outcomes was conducted.

Results: A total of 28 patients presented with signs of acute limb ischaemia, of whom 28.6% were aged <30 days, 46.4% were between one and 12 months and 25% were between one and five years old; 78.6% of the affected limbs were lower limbs. Four patients had resolution of ischaemia upon removal of the vascular access devices. 23 patients received various forms of pharmacological sympathectomy, in addition to conservative therapy. One patient had missing data on the type of sympathectomy that was done. The response to the sympathectomies was: 60.9% good, 8.7% moderate, 8.7% poor and in 21.7% no response. Documented tissue loss related to the ischaemia occurred in six (21.4%) of the 28 patients.

Conclusions: Iatrogenic acute limb ischaemia in children are usually managed without surgical intervention. Pharmacological sympathectomies led to increased blood flow to the affected limb via vasodilatation of collateral vessels, with an added advantage of reducing ischemic pain. The improved blood flow is postulated to avoid and/or minimise

the amount of tissue loss. Pharmacological sympathectomies may, thus, have a role to play in the management of iatrogenic acute limb ischemia in the paediatric population.

Keywords and phrases: Paediatric, acute limb ischaemia, complications of arterial cannulation, treatment algorithms, umbilical artery catheter complications.

MAIN TEXT

10.3 Background

Acute limb ischaemia following vessel cannulation is a recognised and well-documented complication in the paediatric population. Management of the acute limb ischaemia in this patient population is aimed at improving limb blood flow to the affected limb. There are no specific therapies for acute limb ischaemia and published protocols for management of these patients are not inclusive of all the proposed interventions present in the literature.¹⁻⁶

The incidence of complications related to arterial and venous catheterisation in the general paediatric intensive care unit is similar to that found in the adult intensive care setting.^{1, 7} Although uncommon, acute limb ischaemia is a well-recognised complication of blood vessel cannulation in both the adult and paediatric population. The aetiology of acute limb ischaemia is multifactorial and its pathophysiology is not well understood. The proposed theories include vessel spasm following manipulation, intraluminal thrombosis and thrombotic embolisation, and perivascular haematoma, among others.^{1, 2, 4, 5} The natural history of acute limb ischaemia related to catheterisation is unknown, but limb infarction necessitating amputation does occasionally occur. Various therapeutic

measures, including conservative, medical and surgical strategies, are undertaken to try to improve the blood flow to avoid limb infarction and the need for amputation.^{2, 4, 5, 8-12}

10.4 Methodology

Approval was obtained from the Human Research Ethics Committee (HREC) of the University of Cape Town and the management of the Red Cross War Memorial Children's Hospital to review hospital records of the paediatric intensive care unit and cardiothoracic databases from January 2008 to July 2013. The following International Classification of Disease 10th Version (ICD-10) codes and phrases were used in the search of the databases: arterial thrombosis or emboli (T81.71–T81.72), other vascular complications (T81.8), and complications of vascular device not otherwise specified (T81.9).

Patients with acute limb ischaemia secondary to cannulation of arteries, veins or both vessels were identified. All children with acute limb ischaemia not related to vessel cannulation were excluded from the study.

Patients identified from the database search results and those who were referred to the anaesthetic department for an appropriate pharmacological sympathectomy had their folder number entered onto a spreadsheet with corresponding study numbers. Measures to ensure confidentiality of patients were taken. A retrospective folder review was performed and data in Table I was collected from the patients' folders.

Table I. Data to be Collected from Patients' Folders

Demographic data	Age, gender, weight
Admission timeline	Date of admission, date of incident
Admitting diagnosis	ICD10 term and code
Associated conditions	Sepsis, shock, coagulopathy, trauma
Associated therapy	Fluids preceding six hours, blood products, inotropes, vasoconstrictors
Details of limb involvement	Anatomical regions, side
Presenting signs	Pallor, decreased perfusion, decreased pulses, decreased temperature, infarcted skin, pain
Aetiological factors	Venous catheter, arterial catheter, venepuncture, arterial puncture, trauma
Conservative management	Warming, limb elevation, catheter removal, systemic vasodilators, decrease in dose of vasoconstrictors and anticoagulation
Outcome	Resolution, repeat intervention, infarction, amputation

The response to pharmacological sympathectomy (PS) was subjectively graded according to the description recorded in the clinical notes by the attending anaesthetist and was based on the consensus of three reviewers who assessed the clinical record. The responses to PS were graded as follows:

- a. Good: Return of perfusion to the limb evidenced by resolution of skin temperature and colour change compared to the contralateral non-ischemic limb.
- b. Moderate: Resolution of initial signs, with minor differences in appearance of the ischemic limb compared to the non-ischemic.
- c. Poor: Some resolution was thought to have occurred, but signs not completely resolved.
- d. No response: Ischemic limb remained as before the block.

A descriptive analysis of the collected data was conducted using Microsoft Excel (2013) and IBM SPSS Statistics (Version 22) software.

10.5 Results

Thirty-two patients were identified between January 2008 and July 2013. Four patients were excluded from the study, because the cause of the ischaemia was due to meningococcal vasculitis or peripheral embolisation related to other coagulopathies. A total of 28 patients presented with signs of iatrogenic acute limb ischaemia, of whom 28.6% were aged <30 days, 46.4% were between one and 12 months and 25% were between one and five years old. The mechanism of vessel injury was iatrogenic in nature. The weight ranged from 1.4 to 13 kilograms with a mean of 5.18 kilograms. The demographics of the study population are shown in Tables II.

Table II Patient Demographics at Presentation

Variable	Quartiles				
	Minimum	25 th centile	Median	75 th centile	Maximum
Age (weeks)	0.0	0.6	12.8	43.6	195.5
Weight (kg)	1.4	2.1	4.4	7.3	13.0

Table III shows the aetiological groupings of the different admission diagnoses to the paediatric intensive care unit (PICU).

Table III. Aetiological Grouping of Diagnoses

Aetiology Group	Number per Group
Infective	14
Congenital cardiac anomaly	7
Congenital gastrointestinal	6
Toxic ingestion	1
Total	28

Table IV shows the number of patients who presented with shock and sepsis. Sixteen out of 28 patients were in shock and 18 of them were septic, requiring inotropic support.

Table IV. Sepsis vs. Shock Cross Tabulation

			Shock		Total
			No	Yes	
Sepsis	No	Count	7	3	10
		% of Total	25%	11%	36%
	Yes	Count	5	13	18
		% of Total	18%	46%	64%
Total	Count	12	16	28	
	% of Total	43%	57%	100%	

The types of vascular access are shown in Table V. The femoral artery was the most frequently accessed. This corresponds to the highest number of ischemic legs. Twenty five percent of arterial cannulations were on the upper limb.

Table V. Type of Access

Type of Access	Frequency	Percentage
Femoral A-line	15	53.6%
Radial A-line	6	21.4%
A-line Cath. Lab*	3	10.7%
Femoral central venous line	2	7.1%
Brachial A-line	1	3.6%
Umbilical arterial catheter	1	3.6%
Total	28	100%

*A-line = Arterial line

**
Cath. Lab = Catheterisation Laboratory

Four patients had resolution of the signs of ischaemia upon removal of vascular access devices without the need for PS. Twenty-four patients were referred for PS. Only twenty-three patients had clinical records of the type of PS done and the responses to PS. 82% of patients had a caudal block, corresponding with higher incidence of ischaemic lower limbs. All the three upper limb blocks were done under ultrasound guidance. Bupivacaine was the local anaesthetic used in all the PS. The choice of the local anaesthetic was purely based on what is readily available at our State institution. A maximum dose of 0.25% bupivacaine 1ml/kg was used for all the sympathectomies. The types of PS used and their corresponding percentages are shown in Table VI.

Table VI. Therapy*

Therapy	Frequency	Percentage
Caudal	19	82.6%
Axillary block	1	4.3%
Popliteal block	2	8.7%
Interscalene block	1	4.3%
Total	23	100%

*Therapy = Pharmacological Sympathectomy (PS)

Table VII shows the response to PS. Approximately 80% of patients responded to pharmacological sympathectomies. Fourteen patients (60.9%) had good responses, but 5 patients (21.7%) showed no response to PS.

Table VII. Response to Therapy

Response to Therapy	Frequency	Percentage
Good	14	60.9%
Moderate	2	8.7%
Poor response	2	8.7%
No response	5	21.7%
Total	23	100%

Table VIII refers to the patients who had some form of tissue loss and their response to PS. Tissue loss was reported in six patients.

Table VIII. Adverse Outcome and Corresponding Response to Pharmacological Sympathectomy

Recorded Adverse Outcome	Response to PS
Above-knee amputation Amputation of the metatarsal/tarsal joint of right foot Left below-knee amputation	No response
Mid-forearm amputation	Poor response
Self-amputation of necrotic toe	Moderate response
Left small toe amputation	Good response

10.6 Discussion

This review was undertaken to establish the frequency of iatrogenic acute limb ischaemia (IALI) and to assess treatment modalities used in managing this complication at Red Cross War Memorial Children’s Hospital. Currently, there is no specific treatment protocol for the management of this group of patients at our hospital. Patients with non-iatrogenic acute limb ischaemia, threatened or non-viable limbs are referred to surgeons and undergo limb perfusion studies to determine appropriate level of amputation when limb salvage is not an option.¹³

The majority of our study population had arterial line cannulae cited for the purposes of blood sampling for guidance of ventilatory management, repeat blood testing and for titration of vasopressors’ doses. The diagnoses recorded as the reason for admission to the intensive care unit were mostly of infective aetiology, with respiratory infections being the most prevalent. In our study, only three patients (10.7%) had post

catheterisation laboratory complication. This is in stark contrast to other published series where post-cardiac catheterisation complications were the commonest cause of iatrogenic acute limb ischaemia accounting for approximately 90% of cases.²

The most important factors in the outcome of acute limb ischaemia are early diagnosis and institution of appropriate intervention.⁵ Angiogram is the gold standard investigation for confirming arterial occlusion in a child with acute limb ischaemia. In a critically ill patient angiography is not always feasible to perform and has added risks of further vessel cannulation and contrast-induced kidney injury. In this setting, Doppler ultrasound studies are the most favoured investigative tools.^{2, 5} Diagnosis of iatrogenic acute limb ischaemia in our study was largely based on clinical signs such as poikilothermia of the affected limb, reduced capillary refill, changes in skin colour and increased irritability of the patient. Only two patients in our study had ultrasound of the affected limbs. This could be attributed to the lack of protocols or non-availability of expertise at time of diagnosis of IALI.

The management of iatrogenic acute limb ischaemia focuses on improving the perfusion to the affected limb. To achieve this, various treatment modalities have been suggested in the literature. These include conservative (removal of the catheter, warming of the contralateral limb-based on reflex vasodilatation of the ischemic limb, limb elevation), medical (use of topical 2% nitroglycerine ointment,¹⁰ changes in vasoconstrictor therapy, systemic anticoagulation and thrombolysis)^{2, 4, 14} and surgical management (thrombectomies or reconstructions).^{2, 5, 9, 15} The use of PS in the form of neuraxial and

peripheral nerve blocks is well documented^{4,6} but does not necessarily fall under any the aforementioned management strategies.

Anticoagulation of patients forms the backbone of the medical management in most of the protocols.^{2, 4, 5, 8} Even though widely used, the CHEST guidelines on antithrombotic therapy in neonates and children suggest that the evidence for use of anticoagulants in this age group is weak.¹⁶ The authors of these guidelines recommend that, to employ this treatment modality, a multi-disciplinary body consisting of paediatrician/intensivist, paediatric haematologist or adult haematologist experienced in paediatric haematology must be available, among other staff.^{2, 16, 17} Contraindications to antithrombotic therapy include post-major surgery, coagulopathies, heparin-induced thrombocytopenia and various degrees of intraventricular haemorrhage.^{15, 17}

In our study only two patients, both with good response to PS, were found to have thrombus in the popliteal artery and femoral vein, respectively, and were anticoagulated. Heparin infusion and enoxaparin boluses were the agents used. We are unable to report on the doses and duration of the anticoagulation, as this was not captured in our data collection.

The last resort intervention in adults is vascular bypass surgery. However, for patients younger than two and half years old or with a body weight of less than 12.5 kilograms, surgery is only considered when all conservative and medical management strategies have failed. This is because of the poor outcomes and high rates of repaired vessel re-thrombosis in this age group.^{5, 8, 9} Factors that determine what treatment is applied

include time from onset of ischaemia to diagnosis, site of ischaemia, amount of threatened tissue, patient age, size of the affected vessel, and availability of technical expertise for such procedures as nerve block and microvascular surgery.^{1, 2, 4, 8, 15} The average weight for the patients who had tissue loss in our study was 3.5 kilograms. None of the patients had operative intervention as a rescue strategy to prevent tissue loss. Surgical intervention to salvage the limbs was not attempted, probably because the patients were considered to be too small for a good postoperative outcome.⁸

One patient with difficult arterial access had a brachial artery cannulation with subsequent ischaemia of the left arm. Intra-catheter administration of papaverine by the intensivists resulted in a temporary improvement in perfusion. Vessel spasm was thought to be the sole cause of the ischaemia. An ultrasound-guided interscalene brachial plexus block was performed and ischaemia resolved even though arterial cannula was still in-situ for ongoing monitoring.

An umbilical artery catheter (UAC) was used in a 1.5-kilogram preterm baby. Indications and complications of UAC are well documented.^{10, 14} The preterm responded poorly to PS and was referred to the surgeons who carried out a below knee amputation.

Of the four patients who showed either a poor, or no response to therapy, three had considerable tissue loss (Table IX). We found no records of complications directly related to PS in the form of neurovascular bundle injury or local anaesthetic toxicity. Four patients died of causes related to their diagnoses on admission or complications

such as multi-organ failure. We are unaware of any deaths directly linked to the iatrogenic acute limb ischaemia in our study population.

10.6.1 Pathophysiology of Iatrogenic Acute Limb Ischaemia

Pathogenesis of acute limb ischaemia following an iatrogenic manipulation is multifactorial.^{1, 4, 10} Physical obstruction of the artery by thrombus, intra-arterial cannula, spasm of the muscular component of the arterial wall secondary to trauma, transection of arteries and perivascular hematoma are among the most cited causes of arterial vascular insufficiency.^{1, 2, 12, 15, 17} The acute vessel thrombosis is initiated by mechanical damage to the vascular endothelium with subendothelial tissue and collagen exposure to the circulating blood.¹⁵ The exposure of subendothelial tissue brings about the accumulation and activation of platelets on the surface of the catheter and vessel with subsequent interaction with Von Willebrand factor. The result of this interaction is activation and aggregation of platelets to form prothrombotic plugs. The platelets also release vasoactive substances such as adenosine diphosphate and thromboxane A2. Thromboxane A2 is a potent vasoconstrictor which further activates platelets and cause vasospasm. Decreased blood flow distal to the vasospasm and presence of an intra-arterial cannula may promote intravascular thrombus formation. The duration of the arterial spasm is can last four to six hours.^{9, 18} The result of all these events is tissue ischaemia distal to the cannulation site if the collateral circulation is inadequate.

The use of large cannulas in relation to vessel calibre may increase the risk of arterial occlusion. Perivascular haematoma may cause reduced limb perfusion pressure by

arterial compression thereby decreasing distal perfusion pressure or obstruction of the venous drainage.^{5, 9} Critically ill patients often exhibit a prothrombotic state (sepsis, dehydration, polycythaemia and reduced cardiac outputs) that predisposes to thrombosis.^{10, 12, 17}

10.6.2 Argument for use of Sympathectomies in the Treatment of Iatrogenic Acute Limb Ischaemia

Based on the Oxford Centre for Evidence-Based Medicine 2011 levels of evidence, treatment of iatrogenic acute limb ischaemia currently stands at level 4, as there are no randomised controlled trials or systematic reviews on the subject. Despite some evidence of efficacy in the literature, use of pharmacological sympathectomies (PS) is not included in the most referenced treatment protocols and/or is not the first line of management in those that include them.^{2-6, 14, 17}

Although surgical approaches improve limb perfusion,^{5, 17} surgery has attendant risks: transfer of a critically ill child to a theatre, instrumentation of the endothelium in the setting of a hypercoagulable state^{10, 12} and the technical difficulty of working with small vessel calibre.^{9, 15} The decision to proceed to the theatre is driven by evidence of complete vessel occlusion and availability of specialist in microsurgery. This decision is only made upon assessment of vascular function or reserve by such means as angiography or Doppler studies, which may be difficult to interpret in the setting of a critically ill child.^{2, 5, 8, 17}

The use of PS as a treatment strategy for vascular insufficiency first appeared in the literature in 1984. Lagade used stellate ganglion block to treat arterial insufficiency in a 1,600-gram premature infant of a 32 weeks gestation twin pregnancy.¹¹ A few years later, literature was populated by case reports and a series of successful use of neuraxial and peripheral nerve blocks in the management of acute limb ischaemia.^{3, 12, 19–22}

PS using local anaesthetics is a treatment modality that can be used to bridge, or even differentiate between patients who would require medical or surgical care in the absence of angiography or inconclusive Doppler studies. In most cases of iatrogenic acute limb ischaemia, the pathogenesis is that of vasospasm and incomplete vessel occlusion by thrombi.^{10, 19, 20, 21} Therefore, it makes physiological sense to use vasodilatation therapy in the form of the sympathetic blockade as part of the first line treatment. A correctly performed PS that does not achieve any improvement in limb perfusion through vasodilatation of collaterals would imply that the risk of potential tissue loss in that limb is high, and more aggressive therapy such as thrombolysis and/or surgical management is warranted. The duration of action of these blocks range from four to 18 hours on average.²³ Depending on the type of PS used, the vasodilatation usually exceeds the duration of the vessel spasm.^{3, 4, 9, 11, 14}

Children have good collateral circulation and, due the absence of vascular diseases such as atherosclerosis, a good vasodilatory response can be induced compared to the adult population.^{3, 11, 12, 15} PS in this patient population have been shown to improve blood flow by a factor of six on Doppler studies.¹² In addition, PS abolishes the pain and stress

response. The stress response and pain are thought to worsen perfusion in the ischaemic limb by increasing the peripheral vascular resistance through adrenergic mediated vasoconstriction.⁴ PS are also cost effective compared to other treatment modalities²⁷ and can be performed in the ICU at the bedside by a maximum of two people. The real-time visualisation of anatomical structures aided by ultrasound has reduced the failure rates of PS and risk of intra-nerve and intravascular administration of local anaesthetics.^{24, 25} Apart from reduction in complication rates, ultrasound allows for deposition of the highest safe dose of local anaesthetic as close as possible to the nerve or nerve roots for maximal effect and duration of action

Pharmacological sympathectomies are not without complications. These complications are related to injuries to anatomical structures during the procedure, local or systemic infections, and cardiovascular and neurological manifestations of high serum concentrations of local anaesthetics.²⁵ Other factors that increase the risk of complications include the size of the paediatric patient and non use of ultrasound guidance. Neuraxial blocks can cause hypotension; an unwanted event if the patient requires inotropic support.^{21, 25}

In agreement with other published studies,^{2, 4, 5, 8} our audit shows that, in the majority of cases, iatrogenic acute limb ischaemia in the paediatric population of less than 12.5 kilograms is well-managed by non-operative means. Based on the pathogenesis of this complication and the ability of the paediatric vasculature to open collaterals, pharmacological sympathectomies may have a role in the management of the iatrogenic acute limb ischaemia.^{10-12, 15, 18}

10.6.3 Study limitations

1. This is a retrospective audit
2. The record search might have missed patients who met the inclusion criteria.
3. Incomplete data entry for signs of limb ischaemia before and after the intervention, no record of number of attempts at cannulation and time of diagnosis of acute limb ischaemia to the time of intervention.

10.6.4 Our recommendations

1. When managing patients with acute limb ischaemia, clinicians need to be aware of the need for accurate data entry in terms of description of the signs of ischaemia, time of diagnosis, intervention instituted and outcome of the employed management strategy. This needs to be based upon a universally agreed upon description. Unfortunately, one does not currently exist.
2. There is a need for standardised diagnostic criteria based on measurable parameters. We suggest using the following: temperature difference between affected and unaffected areas, capillary refill, blood flow characteristics analysis using Doppler, ultrasound of anatomical region involved to assess integrity and patency of blood vessels.
3. Based on the review of the literature and from our experience, pharmacological sympathectomies have a role to play in the management of IALI in the paediatric population.

4. Patients who show poor or no response should be candidates for more aggressive investigations and appropriate referral to other specialists such as paediatric haematologists and microvascular surgeons if such specialties are available.
5. Use of anticoagulants and thrombolytic agents for management of acute limb ischaemia is well documented in the literature. If no contraindications are noted, they should be considered as part of the medical therapy.
6. A protocol with defined time frames from simple treatment modalities to more aggressive forms is needed.

10.7 Conclusion

Iatrogenic acute limb ischaemia is a recognised complication of vascular access in the paediatric population. Lack of standardised treatment protocol may lead to inadequate therapy and serious consequences for the patient. There is evidence in the literature to suggest that use of pharmacological sympathectomies improves perfusion to the affected limb and enhances patient comfort. From our experience and the literature reviewed, this treatment modality has a role to play, especially in the setting where micro-vascular surgery is technically difficult or specialist expertise is not available. Therefore, we recommend that sympathectomies be considered as part of initial and discriminatory therapy in iatrogenic acute limb ischaemia if no improvement is noticed with conservative management alone. Patients with no or poor response after a correctly placed sympathectomy can be fast-tracked to more aggressive investigation and management strategies.

10.8 References:

1. King MA, Garrison MM, Vavilala MS, Zimmerman JJ, Rivara FP. Complications associated with arterial catheterization in children. *Pediatr Crit Care Med* [Internet]. 2008;9(4):367–71. Available from: http://journals.lww.com/pccmjournal/Fulltext/2008/07000/Complications_associated_with_arterial.2.aspx
2. Kayssi A, Shaikh F, Roche-Nagle G, Brandao LR, Williams SA, Rubin BB. Management of acute limb ischemia in the pediatric population. *J Vasc Surg* [Internet]. Society for Vascular Surgery; 2014;60(1):106–10. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0741521414001530>
3. Hargreaves DM, Spargo PM, Wheeler RA. Caudal blockade in the management of aortic thrombosis following umbilical artery catheterisation. *Anaesthesia* [Internet]. Blackwell Publishing Ltd. 1992 Jun 1;47(6):493–5. Available from: <http://dx.doi.org/10.1111/j.1365-2044.1992.tb02273.x>
4. Taub PJ, O’Connell JP, Singh A, Pinto A, Kapklein M, Goltzman C, et al. Acute ischemia of the lower extremity in the pediatric population: a protocol for management. *Mt Sinai J Med*. 2006;73(8):1074–8.
5. Downey C, Aliu O, Nemir S, Naik-Mathuria B, Hatf DA, Bullocks JM, et al. An algorithmic approach to the management of limb ischemia in infants and young children. *Plast Reconstr Surg* [Internet]. 2013 Mar [cited 2013 Oct 30];131(3):573–81. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23142939>

6. Georgiadis GS, Lazarides MK. Comment on “Management of limb ischaemia in the neonate and infant” (Eur J Vasc Endovasc Surg 2009;38:61-65). A proposed algorithm for optimal results. Eur J Vasc Endovasc Surg [Internet]. 2009 Oct [cited 2013 Aug 17];38(4):531–2. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19608441>
7. Frezza EE, Mezghebe H. Indications and complications of arterial catheter use in surgical or medical intensive care units: analysis of 4932 patients. Am Surg. 1998;64:127–31.
8. Lazarides MK, Georgiadis GS, Papas TT, Gardikis S, Maltezos C. Operative and nonoperative management of children aged 13 years or younger with arterial trauma of the extremities. J Vasc Surg [Internet]. 2006;43(1):72–6. Available from: <http://www.sciencedirect.com/science/article/pii/S0741521405017039>
9. Friedman J, Fabre J, Netscher D, Jaksic T. Treatment of acute neonatal vascular injuries-the utility of multiple interventions. J Pediatr Surg 1999;34:940–945.
10. Baserga M, Mariana C M, Asha Puri M, Augusto Sola M. The use of topical nitroglycerin ointment to treat peripheral tissue ischemia secondary to arterial line complications in neonates. J Perinatol [Internet]. [cited 2013 Aug 19];22(5):416–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12082481>
11. Lagade MR, Poppers PJ. Stellate ganglion block: a therapeutic modality for arterial insufficiency of the arm in premature infants [Internet]. Anesthesiology. 1984. p. 203–4. Available from: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt>

=Citation&list_uids=6465603

12. Sanchez V, Segedin ER, Moser M, Pallares VS. Role of lumbar sympathectomy in the pediatric intensive care unit. *Anesth Analg* [Internet]. 1988 Aug;67(8):794–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3394971>
13. Brink A, Cox S, Mann M D, Rode H. The role of limb perfusion studies in the paediatric ischaemic limb. *S. Afr. j. surg.* [Internet]. 2014 Jan [cited 2016 Apr 07] ; 52(1): 13-17. Available from: http://www.scielo.org.za/scielo.php?script=sci_arttext&pid=S0038-23612014000100004&lng=en
14. Arshad a, McCarthy MJ. Management of limb ischaemia in the neonate and infant. *Eur J Vasc Endovasc Surg* [Internet]. Elsevier Ltd; 2009 Jul [cited 2014 Jan 1];38(1):61–5. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19362027>
15. Hobman J, Khandwala A, Batchelor A. Management of iatrogenic lower limb ischaemia in children. *Br J Plast Surg* [Internet]. 2004 Apr [cited 2013 Oct 30];57(3):245–51. Available from: <http://www.sciencedirect.com/science/article/pii/S0007122603005666>
16. Monagle P, Chan AKC, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Göttl U, et al. Antithrombotic Therapy in Neonates and Children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* [Internet]. American College of Chest Physicians; 2012 Feb 23;141(2 Suppl):e737S – e801S. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278066/>

17. Coombs CJ, Richardson PW, Dowling GJ, Johnstone BR, Monagle P. Brachial artery thrombosis in infants: an algorithm for limb salvage. *Plast Reconstr Surg* [Internet]. Lippincott Williams & Wilkins; 2006 [cited 2013 Nov 10];117(5):1481–8. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16641716>
18. Flanigan DP, Keifer TJ, Schuler JJ, Ryan TJ, Castronuovo JJ. Experience with iatrogenic pediatric vascular injuries. Incidence, etiology, management, and results. *Ann Surg*. 1983;198(4):430–42.
19. Avenant C, Kirsten G. Anterior Interscalene Approach To the Brachial Plexus Using a Nerve Stimulator As Rescue Therapy for Arterial Occlusion Due To an Indwelling Brachial Artery Cannula in Infants . *South African J Reg Anaesth* [Internet]. :9–12. Available from: http://sajra.co.za/articles/February_01_AnteriorIntersaclene.pdf
20. Breschan C, Kraschl R, Jost R, Marhofer P, Likar R. Axillary brachial plexus block for treatment of severe forearm ischemia after arterial cannulation in an extremely low birth-weight infant. *Pediatr Anesth* [Internet]. Blackwell Publishing Ltd; 2004 Aug 1;14(8):681–4. Available from: <http://dx.doi.org/10.1111/j.1460-9592.2004.01282.x>
21. Tobias JD. Therapeutic application of regional anaesthesia. *Paediatric Anaesth* . 2002;12:272–277.
22. Dalens B. Lower extremity nerve blocks in paediatric patients. *J New York Sch Reg Anesth*. 2006;16–27.

23. Delvi MB. Ultrasound-guided peripheral and truncal blocks in pediatric patients. Saudi J Anaesth [Internet]. India: Medknow Publications; 2011;5(2):208–16. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3139317/>
24. Warman P, Bch BM, Anaesthesia R, Chb MB, Anaesthesia C, Medicine P. Best Practice & Research Clinical Anaesthesiology Ultrasound-guided nerve blocks : efficacy and safety. Best Pract Res Clin Anaesthesiol [Internet]. Elsevier Ltd; 2009;23(3):313–26. Available from: <http://dx.doi.org/10.1016/j.bpa.2009.02.004>
25. Jeng CL, Torrillo TM, Rosenblatt MA. Complications of peripheral nerve blocks. Br J Anaesth. 2010;105(Suppl 1):i97–i107.
26. Macario A. What does one minute of operating room time cost? J Clin Anesth [Internet]. 2010 Jun;22(4):233–6. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0952818010000917>

11 APPENDIX

11.1 Appendix 1. Data Collection Form

ADDENDUM ONE : DATA COLLECTION SHEET						
Study No: _____		Date of review: _____				
Patient Details	Complete by hand when table not available Name: _____ Birth : _____ Age: _____ Folder Number : _____ Sex : _____					
	Weight:					
Date of Admission: _____		Date of Accident : _____				
Diagnosis on Admission :						

ICD 10 CODE:						

Comorbid state :						
	Shock :	Sepsis :	Coagulopathy:	Trauma:		
Associated Medical Therapy:	Inotrope or Vasoconstrictor:	Type :	Dose:			
		Type:	Dose:			
		Type:	Dose:			
(6 hours prior to incident)	Perioperative Fluids (ml)	Crystalloid: _____ ml/kg:	Colloid : _____ ml/kg:	FFP : _____ ml/kg:		
		Whole blood: _____ ml/kg:	Packed cell: _____ ml/kg:	Platelets : _____ ml/kg:		
Limb involved:	Arm:	Hand:	Finger:	Leg:	Foot:	Toe:
Side of Body:	Right:	Left:	Both:			
Presenting Complaint:	Decreased Perfusion:		Change in Colour:			
Aetiological Factors:	Venipuncture:	Arterial puncture:	Compressive Dressing:			
	Venous cannula:	Gauge:	Arterial Cannula:	(Gauge)		
	Comment if difficult insertion: _____					
	Comment on site of insertion: _____					
Conservative Management:	Warm	Elevation	Catheter removal			
	Systemic vasodilator	Change in vasoconstrictor				
Interventional Management:	Intra-arterial drug	Peri-arterial drug	Embolectomy			
	Regional Anaesthetic :	What:	Drug:			
Outcome:	Resolution	Repeat intervention	Infarction	Amputation		
	Comment:					

11.2 Appendix 2. Diagnosis on admission to Paediatric Intensive Care Unit

Diagnosis	Frequency	Percent
Gastroenteritis	4	7.1
Pneumonia (bacterial)	3	7.1
Adenovirus pneumonia /ARDS	2	3.6
Meningitis	1	3.6
ALCAPA/pneumonia/Acute Gastroenteritis	1	3.6
AVSD, PDA	1	3.6
Biliary Atresia	1	3.6
Bowel Perforation/NEC	2	3.6
Bronchopneumonia/MOD	1	3.6
Coarctation of Aorta/PDA/TOF	1	3.6
Measles/pneumonia	2	3.6
Paraffin ingest	1	3.6
PDA	1	3.6
Redo Pyloromyotomy	1	3.6
Status epilepsy/bronchopneumonia	1	3.6
TAPVD	1	3.6
Tracheal Oesophageal Fistula (post repair)	1	3.6
TOF/duodenal atresia	1	3.6
Tricuspid Atresia/ASD/VSD	1	3.6
Sub total	27	96.4
Missing data	1	3.6
Total	28	100.0

ARDS=Acute Respiratory Distress Syndrome, ALCAPA=Anomalous Left Coronary Artery From the Pulmonary Artery,

AVSD=Atrioventricular Septal Defect, PDA=Patent Ductus Arteriosus, NEC=Necrotising Enterocolitis,

MOD=Multi-organs Dysfunction, TOF=Tetralogy of Fallot, TAPVD=Total Anomalous Pulmonary Venous Drainage,

ASD=Atrial Septal Defect, VSD=Ventricular Septal Defect

11.3 Appendix 3. Ethics Approval Letter



UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee



Room E52-24 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
Email: shuretta.thomas@uct.ac.za
Website: <http://www.health.uct.ac.za/fhs/research/humanethics/forms>

17 June 2014

HREC REF: 391/2014

Dr O Hodges
Anaesthesia
D23, NGSH

Dear Dr Hodges

PROJECT TITLE: AUDIT OF ACUTE LIMB ISCHAEMIA IN A PAEDIATRIC INTENSIVE CARE UNIT Sub-study linked to 214/2010 (MMed-candidate-Dr J Mumba)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th June 2015

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

We acknowledge that the MMed student, Dr Jesse Mumba is also involved in this study.

Please quote the HREC reference no in all your correspondence.

Yours sincerely

Signed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.

Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

HREC 391/2014

11.4 Appendix 4. Request to Conduct Research



UNIVERSITY OF CAPE TOWN



RED CROSS WAR
MEMORIAL CHILDREN'S HOSPITAL

D23, Department of Anaesthesia
University of Cape Town
Anzio Road
Observatory
7925

20 April 2010

Prof H. Zar
Departmental Scientific Committee
Department of Paediatrics
Institute of Child Health
Red Cross War Memorial Children's Hospital
Klipfontein Road
Rondebosch

Dear Prof Zar

PROJECT TITLE: Audit of Acute Limb Ischaemia in a Paediatric Intensive Care Unit

We would like to perform the above-mentioned audit at Red Cross War Memorial Children's Hospital. I have discussed the matter with Dr Lesley Henley, at Red Cross and she has suggested that the protocol be submitted for an expedited review. I would be grateful if you would review the attached protocol.

Please find attached the following documents:

1. Completed FHS002 (C1) Form
2. Completed FHS013 New protocol application form
3. Audit Protocol synopsis x 2
4. Audit Protocol, including data collection sheet x 2

Yours Sincerely

Signed

Owen Hodges MBChB, FCA (SA)

11.5 Appendix 5. Approval to Conduct Research



Departement van Gesondheid
Department of Health
iSebe lezewMpilo



Verwysing:	RESEARCH	Telefoon:	
Reference:		Telephone:	(021) 658 5788
Isalathiso:		Ifowuni:	
Navrae:		Fax:	(021) 658 5166
Enquiries:	Dr. T. Blake	Email:	Tblake@pgwc.gov.za
Datum:			
Date:			

Dear

I

Your research proposal is hereby acknowledged.

The following information / documentation (if applicable) is required before permission can be granted to conduct your research can be approved:

1.	Letter requesting permission to conduct the study / research.
2.	Ethics committee approval letter.
3.	Study dates: starting and end dates.
4.	Proof of registration as student at University.
5.	Letter of support from your supervisor (students).
6.	Acknowledgement that all patient information will be treated as confidential.
7.	Exactly where in the hospital will the study be conducted e.g. review of folders, outpatients etc. The relevant areas will need to be informed of your intention and that permission has been granted by the hospital for the research.
8.	That a copy of your final document will be made available on completion of your project.
9.	Budget and resources for the research to be explicit.

Signed: T. Blake

Dr. T. Blake
Senior Medical Superintendent

12 INSTRUCTIONS TO AUTHORS

South African Journal of Anaesthesia and Analgesia

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All articles must have a title page with the following information and in this particular order: Title of the article; surname, initials, qualifications and affiliation of each author; The name, postal address, e-mail address and telephonic contact details of the corresponding author and at least 5 keywords.

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Acknowledgements

In a separate section, acknowledge any financial support received or possible conflict of interest. This section may also be used to acknowledge substantial contributions to the research or preparation of the manuscript made by persons other than the authors.

References

Cite references in numerical order in the text, in superscript format (Format> Font> Click superscript). Please do not use brackets or do not use the foot note function of MS Word. In the References section, references must be typed double-spaced and numbered consecutively in the order in which they are cited, not alphabetically.

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List all authors when there are six or fewer; when there are seven or more, list the first six, then ";et al."; When citing URLs to web documents, place in the reference list, and use the following format: Authors of document (if available). Title of document (if available). URL. (Accessed [date]).

The following are sample references:

1. Jun BC, Song SW, Park CS, Lee DH, Cho KJ, Cho JH. The analysis of maxillary sinus aeration according to aging process: volume assessment by 3-dimensional reconstruction by high-resolution CT scanning. *Otolaryngol Head Neck Surg*. 2005 Mar;132(3):429-34.
2. Polgreen PM, Diekema DJ, Vandenberg J, Wiblin RT, Chen YY, David S, et al. Risk factors for groin wound infection after femoral artery catheterization: a case-control study. *Infect Control Hosp Epidemiol* [Internet]. 2006 Jan [cited 2007 Jan 5];27(1):34-7. Available from: <http://www.journals.uchicago.edu/ICHE/journal/issues/v27n1/2004069/2004069.web.pdf>

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Tables should be self-explanatory, clearly organised, and supplemental to the text of the manuscript. Each table should include a clear descriptive title on top and numbered in Roman numerals (I, II, etc) in order of its appearance as called out in text. Tables must be inserted in the correct position in the text. Authors should place explanatory matter in footnotes, not in the heading. Explain in footnotes all non-standard abbreviations.

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6. Ethics committee approval has been obtained for original studies and is clearly stated in the methodology.
7. A conflict of interest statement has been included where appropriate.
8. The submission adheres to the instructions to authors in terms of all technical aspects of the manuscript.

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6. There must be an abstract and keywords.
7. References must strictly be in Vancouver format. (Reference numbers must be strictly numerical and be typed in superscript, not be in brackets and must be placed AFTER the full stop or comma.)
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