Journal of Plastic, Reconstructive & Aesthetic Surgery (2016) 69, 381–386

JPRAS
An International Journal of Surgical Reconstruction
www.JPRASurg.com

Serum levels of renin, angiotensin-converting enzyme and angiotensin II in patients treated by surgical excision, propranolol and captopril for problematic proliferating infantile haemangioma

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Received 20 May 2015; accepted 15 October 2015

KEYWORDS
Renin–angiotensin system;
Infantile haemangioma;
Angiotensin-converting enzyme;
Angiotensin II;
Plasma renin activity

Summary The role of the renin–angiotensin system (RAS) in the biology of infantile haemangioma (IH) and its accelerated involution induced by β-blockers was first proposed in 2010. This led to the first clinical trial in 2012 using low-dose captopril, an angiotensin-converting enzyme (ACE) inhibitor, demonstrating a similar response in these tumours. This study aimed to compare serial serum levels of the components of the RAS in patients before and after surgical excision, propranolol or captopril treatment for problematic proliferating IH.

Patients with problematic proliferating IH underwent measurements of serum levels of plasma renin activity (PRA), ACE and angiotensin II (ATII) before, and 1–2 and 6 months following surgical excision, propranolol or captopril treatment.

This study included 27 patients undergoing surgical excision ($n = 8$), propranolol ($n = 11$) and captopril ($n = 8$) treatment. Treatment with either surgical excision or propranolol resulted in significant decrease in the mean levels of PRA. Surgical excision or captopril treatment led to significant decline in the mean levels of ATII. All three treatment modalities had no significant effect on the mean levels of ACE.

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http://dx.doi.org/10.1016/j.bjps.2015.10.020

This study demonstrates the effect of surgical excision, propranolol and captopril treatment in lowering the levels of PRA and ATII, but not ACE, supporting a mechanistic role for the RAS in the biology of IH.

Introduction

Infantile haemangioma (IH), the most common tumour in infancy, affects 4—10% of infants.[1,2] IH has a preponderance for Caucasians, females and premature infants.[2] It is typified by rapid proliferation during infancy, followed by spontaneous involution over the next 5—10 years, often leaving a fibro-fatty residuum.[3]

The role of stem cells in the pathogenesis of IH has been recently reviewed[2], including their interactions within a cytokine-rich milieu, conducive for the initial rapid proliferation of a phenotypic haemogenic endothelium,[4] followed by slow en masse differentiation towards a predominantly mesenchymal-derived tissue.[5]

During infancy, 4—10% of IH require intervention.[6—9] In 2008, two independent French groups serendipitously observed β-blockers, propranolol and acebutolol caused accelerated involution of IH.[10,11] Propranolol is now the preferred treatment for problematic proliferating IH worldwide.[2,12] However, the precise mechanism of action remains to be fully elucidated. A recent study has demonstrated the involvement of the renin—angiotensin system (RAS) in the biology of IH.[13] This is based on the expression of angiotensin-converting enzyme (ACE) and angiotensin II receptor 2 (ATIIR2) on the endothelium of proliferating IH, as well as the observed effect of exogenous angiotensin II (ATII), the downstream vasoactive peptide of the RAS, in promoting in vitro proliferation in IH-derived cells.[13,14]

Serum levels of plasma renin activity (PRA) are approximately five-fold that of adults within the first 3 months of life, tapering to three-fold at 3—12 months of age, two-fold at 1—4 years of age and gradually reducing to normal adult levels from 8 years of age.[15] The tapering levels of PRA from birth through infancy and childhood mirror the programmed biologic behaviour of IH. Higher levels of renin have also been observed in Caucasians (compared with Blacks), females (compared with males) and premature (compared with term) infants; the demographic groups with higher incidence of IH.[13,16] Similarly, serum levels of ATII are three-fold that of adults within the first 3 months of life, reducing to adult levels at 4 years of age.[15] By contrast, serum levels of ACE increase gradually with age, reaching adult levels at around 4 years of age.[15]

Physiologically, renin coverts angiotensinogen to angiotensin I, which is then converted to ATII by ACE.[17] β-blockers reduce the levels of renin, and indirectly lead to reduced availability of downstream ATII, to ATIIR2.[18] The involvement of the RAS in the biology of IH is further supported by the demonstration of accelerated involution of this tumour induced by low-dose captopril, an ACE inhibitor.[19]

In certain anatomic sites where acceptable and/or hidden resultant scars can be achieved, surgical excision[20] remains an effective treatment for discrete problematic proliferating IH.

This study investigated changes in serum levels of renin, ACE and ATII in patients undergoing surgical excision, propranolol or captopril treatment for problematic proliferating IH.

Patients and methods

This study, approved by the New Zealand Central Health and Disability Ethics Committee (ref. no. 13/CEN/130 & CEN12/06/023), prospectively recruited patients with problematic proliferating IH aged 2—12 months from our Vascular Anomalies Centre. The demographic data of the patients and the characteristics of their problematic proliferating IHs were recorded.

In certain anatomic sites where acceptable and/or hidden resultant scars can be achieved, surgical excision was performed on patients with discrete problematic proliferating IH. Serial blood samples were taken prospectively from these patients and those who underwent propranolol or captopril treatment. Propranolol or captopril was administered to patients with problematic proliferating IH for which surgical excision was deemed inappropriate. The patients who underwent propranolol treatment were part of a study reported previously,[14] while those who underwent captopril treatment were part of an observational clinical trial reported previously.[19] Results of retrospective analysis of the serum levels of renin, AII and ACE from blood taken prospectively from patients who underwent surgical excision, or propranolol treatment[14] or captopril treatment[19] for problematic proliferating IH, were the subject of the current report.

Treatments with propranolol[14] and captopril[19] were instituted according to the regimens previously reported.

Propranolol was started at 0.5 mg/kg/day, administered in two divided doses and increased to 1 mg/kg/day after 24 h. Patients were reviewed after 1 week, and the dosage was increased to 1.5 mg/kg/day. In some cases, the dosage was increased to a maximum of 2 mg/kg/day to achieve accelerated involution. Treatment was maintained for an average of 9.3 months with the continuation of the existing dose until an average age of 14.2 months.[14]

Captopril was initiated at 0.1 mg/kg initial dose, followed by 0.15 mg/kg once in 8 h for 24 h, then 0.3 mg/kg once in 8 h for the next 24 h. Patients were reviewed 1 week later, and the dosage was increased to 0.5 mg/kg every 8 h. Treatment was stopped after 14 months.[19]

Patients undergoing propranolol or captopril treatment were reviewed at 1 month and then bi-monthly, with a full