Intralesional Bleomycin treatment for Vascular malformations – A Systematic Review

(intended researchers working on systematic review) S.E.R. Horbach MD, I. Rigter MSc, J.H. Sillevis Smitt MD PhD, W. Middelkamp Hup MD PhD, J.A. Reekers MD PhD, M. Koelemay MD PhD, Ph.I. Spuls MD PhD, C.M.A.M. van der Horst MD PhD

Department of Plastic, reconstructive and hand surgery, Academic Medical Center, Amsterdam, The Netherlands.
Department of Dermatology, Academic Medical Center, Amsterdam, The Netherlands.
Department of Vascular Surgery, Academic Medical Center, Amsterdam, The Netherlands.
Department of Interventional Radiology, Academic Medical Center, Amsterdam, The Netherlands.
Department of Hospital Pharmacy, Academic Medical Center, Amsterdam, The Netherlands.

Summary

Introduction

Bleomycins are a family of glycopeptide antibiotics, originally isolated from the fungus Steptomyces verticillus. (1) Bleomycin A2 and B2 are the principle components for clinical use. In the late 1960’s and 1970’s bleomycin became popular as a potent antitumoural agent in the treatment of various types of cancer, including malignant lymphoma, squamous cell carcinoma of the skin and thyroid carcinoma. (2-4) Nowadays, the use of intralesional bleomycin injections (IBI) has gained popularity as a treatment option for a variety of (sub)cutaneous tumors such as warts, hypertrophic scars and several types of cutaneous malignancies. (5, 6)

Since 1977 the intralesional use of bleomycins (including bleomycin A5, also known as pingyangmycin) have also been suggested for the treatment of vascular and lymphatic lesions, first used in the treatment of cystic hygroma in children. (7) Vascular anomalies can be categorized in vascular tumors with endothelial hyperplasia (such as hemangiomas) and congenital vascular malformations which occur as the result of an error in the embryological development. (8) These two categories of vascular anomalies should not be confused, since they are considered as distinct entities with different therapeutic options and prognosis. In general, hemangiomas grow rapidly during early infancy and by the age of 7 years 70% of these lesions show spontaneous complete involution. In the contrary, vascular malformations are present at birth and grow proportionally with age (8, 9), which is why a great proportion of malformations requires treatment sometime during life.

Vascular malformations can be of arteriovenous (AVM), venous (VM), lymphatic (LM), capillary (CM) or mixed origin, and can be divided in low-flow and high-flow malformations based on the arterial component. (10-12) For each type of vascular malformation a wide range of therapeutic modalities is available and used in daily practice. However, due to a lack of high quality evidence, the optimal
treatment is still not identified. The choice for a specific therapy is often subject to the treating physician’s preference and education. In recent years, intralesional bleomycin injections have been used in vascular malformations with clinically observed promising effects and low complication rates. The exact working mechanism is poorly understood, but fibrosis and endothelial damage are supposed to play an important role. However, the development of pulmonary fibrosis is feared since this condition is associated with high doses of systemic bleomycin in the treatment of malignancies.

**Purpose**

With this systematic review of literature we aim to reveal the efficacy and safety of intralesional bleomycin injections in the treatment of patients with vascular malformations, specified for type of vascular malformation. This will be the first study that systematically collects and analyzes all data on the outcome of bleomycin treatment in vascular malformations.

**Methods**

Data collection and analysis in this systematic review were performed according to the guidelines of the PRISMA statement 2009.(13) A research protocol was established in advance in collaboration with our multidisciplinary research team at the Academic Medical Center Amsterdam and was registered at PROSPERO, an international prospective register of systematic reviews (http://www.crd.york.ac.uk/PROSPERO/).

**Search strategy**

PubMed and EMBASE bibliographic databases were searched for studies reporting the outcome of intralesional bleomycin injections in vascular malformations in the past 20 years. The search strategy included a combination of (MeSH) terms such as vascular malformation, bleomycin and synonyms (table 1) and was peer reviewed by an informational specialist at the Academic Medical Center Amsterdam. The PubMed function ‘Cited references’ and reference lists of all included articles were screened for additional relevant literature. Databases of registered clinical trials (Cochrane central register of controlled trials [CENTRAL], www.controlled-trials.com, www.clinicaltrials.gov and WHO International Clinical Trials Register Platform [ICTRP]) were screened for ongoing trials regarding the use of bleomycin in vascular malformations. A database of retrieved articles was made using EndNote X7 (Thomson Reuters).

<table>
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<tr>
<th>PubMed September 2014</th>
<th>EMBASE September 2014</th>
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<tr>
<td>(&quot;Bleomycin&quot;[Mesh] OR pingyangmycin[tiab] OR pingyangmycin[ot] OR bleomycin[tiab] OR bleomycin[ot]) AND (&quot;Vascular Malformations&quot;[Mesh] OR &quot;Central Nervous System Vascular Malformations&quot;[Mesh] OR &quot;Congenital Lipomatous Overgrowth, Vascular)</td>
<td>exp bleomycin/ or (pingyangmycin or pingyangmycin OR bleomycin or bleomycin).ti,ab,kw. AND exp congenital blood vessel malformation/ or central nervous system malformation/ OR ((vascular adj3 malformation*) or (venous adj3 malformation*) or (arteriovenous adj3 malformation*) or (lymphatic adj3 malformation*) or (venous adj3 malformation*) or (lymphatic adj3 malformation*) or (lymphatic adj3 malformation*))</td>
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adj3 malformation*) or (cystic adj3 hygroma).ti,ab,kw.

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Table 1. Search strategy PubMed (MEDLINE) and EMBASE

Study selection

Only original studies reporting one or more predefined outcome measures of bleomycin therapy for vascular malformations in a group of at least 10 patients were included. Outcome measures were predefined as minor and major complications (including pulmonary fibrosis), size reduction, relief of symptoms, patient satisfaction and quality of life. Papers published before 1995 were excluded, since the currently used classification for vascular malformations was officially adopted in 1996 by the International Society for the Study of Vascular Anomalies(14). Before then, the nomenclature of vascular malformations was subject of debate and various classifications were used for research purposes. Articles in non-English language were excluded if the article was unlikely to meet all inclusion criteria, based on the English abstract. If the English abstract was relevant, the paper was translated and its full-text was screened. Studies reporting outcome of combination therapy of bleomycin with other sclerosing agents or dexamethason were excluded to prevent bias arising from co-medication as a confounding factor. All inclusion and exclusion criteria are shown in table 2. The first selection was made based on title and abstract by two blinded authors (S.H. and I.R.). All remaining full-text articles were analyzed for eligibility by two independent blinded researchers (S.H. and I.R.). There was no blinding to authorship or journal. If eligibility was doubtful, articles were discussed by the investigators (S.H., I.R. and C.H.) and were in- or excluded based on consensus.

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tr>
<td>✓ All vascular malformations</td>
<td>x No full-text journal article published (or finished and waiting for publication)</td>
</tr>
<tr>
<td>✓ Patients treated with bleomycin n≥10</td>
<td>x Articles researching bleomycin treatment in hemangiomas</td>
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<tr>
<td>✓ Publication year ≥1995</td>
<td>x Articles researching a combination of (sclerosing) therapies</td>
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<tr>
<td>✓ Follow-up ≥ 6 months</td>
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<tr>
<td>✓ Only original studies</td>
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<td>✓ At least 1 predefined outcome measure</td>
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### Data Extraction and Data Analysis

Relevant data from each included study was extracted by two independent researchers (S.H. and I.R.) and categorized based on (1) Study information (authors, publication year, journal, country) number of patients, (2) type of vascular malformation, (3) number of patients, (4) age, (5) presenting symptoms (categories: pain, dysfunction, ulceration/bleeding, cosmetic disapproval) (6) size of lesion, (7) dose bleomycin/pingyangmycin, (8) treatment sessions, (9) follow-up, (10) time of measurement (11) outcome measures and (12) main results.

The quality of included articles was assessed by two blinded authors (S.H. and I.R.) using the Effective Public Health Practice Practice Project (EPHPP) Quality assessment tool for quantitative studies. This tool evaluates quality of evidence from different study designs such as RCT’s and observational studies. Various domains are addressed: [1] selection bias, [2] study design, [3] confounders, [4] blinding, [5] data collection methods and [5] withdrawals and drop-outs. Each domain is rated as ‘strong’ (3 points), ‘moderate’ (2 points) or weak (1 point). The paper was rated ‘strong’ if none of the domains were assessed as weak, ‘moderate’ if there was a maximum of one weak rating, and ‘weak’ if there were two or more weak ratings.(15) Any disagreement between the assessors was resolved by consensus.

Obtained data will be displayed in patient characteristics and study characteristics tables. If appropriate (homogenous outcome measures and study protocols), data will be pooled. Data of lymphatic, venous, capillary and arteriovenous malformations will be analyzed separately.

### Complete reference list


