Bleomycin sclerotherapy in congenital lymphatic and vascular malformations of head and neck

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Summary Bleomycin is an established antineoplastic drug, but recently some attempts were made to inject it locally as a sclerosing agent in cases of congenital lymphatic malformations. We present the outcome of this treatment modality tried on 10 paediatric cases of whom 9 had such malformation in the cervical region and one in the parotid region. Seven of these cases had congenital lymphatic malformation while three had haemodynamically less active congenital vascular malformation. All these children were subjected to percutaneous intralesional administration of bleomycin. The size of swelling reduced by 50% or more in seven patients out of which three showed complete or near complete response. There were no major deleterious side effects.

1. Introduction

Surgical excision has been the favoured treatment modality for congenital lymphatic and vascular malformation for quite some time. Since the surgical excision often results in residual pathology, infection and scarring, percutaneous sclerotherapy has been attempted by a few surgeons for such swellings. We have encountered complications with surgical excisions and sclerotherapy using hypertonic saline. Ten years ago a sudden death on the third day of the second injection of hypertonic saline in a 2-year-old child with lymphangioma involving neck and oropharynx, prompted us to abandon sclerotherapy and resort to surgical excision. But even the surgical excisions performed thereafter resulted in wound infections and bad scars on the neck. So we looked for other sclerosing agents with minimal side effects. Various agents like bleomycin, alcoholic solution of Zein (Ethibloc) and OK432 have now been used for percutaneous sclerotherapy [1–3]. Because of the low cost and easy availability, we tried bleomycin sclerotherapy as a first line management on 10 children of congenital lymphatic and vascular malformations in the last 2 years. This produced encouraging results.
About 75% of lymphangiomas occur in the region of head and neck [4]. Thirty-five percent of all lymphangiomas occur in cheek, tongue and floor of the mouth, 25% in neck, and 15% in axilla and they together constitute 0.5% of all neck lumps [5]. Two out of 3 are noted at birth and 9 out of 10 before the second year of life. These swellings may assume a massive size and cause compression on adjoining vital structures such as trachea, oesophagus or major vessels and nerves of the neck. It is usually a multilocular swelling with individual cysts varying from 1 mm to 5 cm in diameter that may communicate with one another. These cysts contain clear or straw coloured serous fluid that may be blood stained. Mulliken and Glowacki have classified congenital vascular lesions on the basis of their clinical and histological characteristics into haemangioma and vascular malformations [6]. The vascular malformations are always present at birth, whereas haemangiomas mostly manifest during the first month of life and are usually not seen at birth. Unlike haemangiomas, the vascular malformations grow proportionally in size with the growth of the body and never regress spontaneously. Congenital vascular malformations can be arterial, capillary, venous, lymphatic or their combinations. They are collection of abnormal vessels with normal mast cell count and endothelium. As assessed haemodynamically the vascular malformations can be further divided into high flow or low flow lesions [7]. We prefer the term ‘haemodynamically less active’ for the ‘low flow’ lesions.

2. Materials and methods

Ten patients of lymphangiomas (cystic hygroma) or haemodynamically less active congenital vascular malformations were included in this study. All patients were followed up on haemogram, renal function tests and chest X-ray during the course of their treatment.

All patients underwent a CT scan, three MRI and two were subjected to MR angiography. An informed consent was taken from the parents before the commencement of sclerotherapy. The procedure was performed under sedation and local anaesthesia. Before injecting bleomycin, the lesion was aspirated at one to four sites and in three patients the aspirate was frank blood at more than one site. These lesions were found to be vascular malformations of lymphovenous type with less haemodynamic activity which was confirmed on MRI and MR angiography. In others the aspiration either yielded straw coloured fluid or it was dry.

The dose of bleomycin administered was 1 mg/kg body weight (maximum dose <6 mg/kg) given at an interval of 2 weeks in a solution of 1 mg/ml in large lesions and 2 mg/ml in smaller lesions. A 23 gauge needle was used and the injection was given at one to four sites. In two patients the bleomycin was injected under ultrasonographic guidance.

This procedure required 1 day’s admission in the hospital for observation. After injection the patients were given a course of antibiotics and analgesics. They were followed on a weekly interval and the procedure was repeated after 2 weeks or more with total sessions of sclerotherapy ranging between 3 and 5.

3. Results

Out of 10 patients 9 were less than 5 years of age. In nine patients the lesion was confined to the neck. Three belonged to the category of congenital

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Site</th>
<th>Size (cm)</th>
<th>Lesion</th>
<th>Total number of sclerotherapies</th>
<th>Outcome</th>
<th>Surgery</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5 yrs</td>
<td>M</td>
<td>Neck</td>
<td>8 × 9</td>
<td>LGM</td>
<td>3</td>
<td>Complete</td>
<td>Nil</td>
<td>2 yrs</td>
</tr>
<tr>
<td>2</td>
<td>8 mths</td>
<td>M</td>
<td>Neck (right)</td>
<td>6 × 7</td>
<td>LGM</td>
<td>5</td>
<td>&gt;50% reduction</td>
<td>Excision</td>
<td>6 mths</td>
</tr>
<tr>
<td>3</td>
<td>4 yrs</td>
<td>M</td>
<td>Neck (left)</td>
<td>6 × 5</td>
<td>LGM</td>
<td>5</td>
<td>50% reduction</td>
<td>Tracheostomy and planned excision</td>
<td>6 mths</td>
</tr>
<tr>
<td>4</td>
<td>10 yrs</td>
<td>F</td>
<td>Neck (left)</td>
<td>5 × 5</td>
<td>LGM</td>
<td>3</td>
<td>25% reduction</td>
<td>Nil</td>
<td>6 mths</td>
</tr>
<tr>
<td>5</td>
<td>4 yrs</td>
<td>M</td>
<td>Neck (left)</td>
<td>8 × 10</td>
<td>LGM</td>
<td>3</td>
<td>25% reduction</td>
<td>Excision</td>
<td>2 mths</td>
</tr>
<tr>
<td>6</td>
<td>4 yrs</td>
<td>M</td>
<td>Neck (right)</td>
<td>6 × 10</td>
<td>LGM</td>
<td>5</td>
<td>Complete</td>
<td>Nil</td>
<td>2 yrs</td>
</tr>
<tr>
<td>7</td>
<td>6 mths</td>
<td>M</td>
<td>Left parotid region</td>
<td>6 × 7</td>
<td>CVM</td>
<td>3</td>
<td>75% reduction</td>
<td>Nil</td>
<td>4 mths</td>
</tr>
<tr>
<td>8</td>
<td>2 yrs</td>
<td>F</td>
<td>Neck (right)</td>
<td>6 × 7</td>
<td>LGM</td>
<td>3</td>
<td>25% reduction</td>
<td>Nil</td>
<td>6 mths</td>
</tr>
<tr>
<td>9</td>
<td>3 yrs</td>
<td>M</td>
<td>Neck (right)</td>
<td>4 × 6</td>
<td>CVM</td>
<td>3</td>
<td>50% reduction</td>
<td>Nil</td>
<td>6 mths</td>
</tr>
<tr>
<td>10</td>
<td>2 mths</td>
<td>F</td>
<td>Neck (right)</td>
<td>8 × 6</td>
<td>CVM</td>
<td>3</td>
<td>Near complete</td>
<td>Nil</td>
<td>6 mths</td>
</tr>
</tbody>
</table>

Abbreviations: LGM, lymphangioma; cm, centimetres; CVM, congenital vascular malformation; mths, months; yrs, years.
vascular malformations and seven to lymphatic malformations (Table 1). All the seven lymphangiomaticous lesions were lymphatic malformations of the Type-I category according to the classification suggested by McGill and Mulliken [8].

The size of the swelling reduced by 50% or more in seven patients, with three showing a complete or near complete response (Figs. 1—4). No major complications were observed during the course of treatment apart from local inflammation in four and residual swellings in seven patients. Three patients underwent surgical excision for their residual swellings.

4. Discussion

Lymphangiomas can be classified into three types: capillary, cavernous and cystic. Embryologically these are thought to arise from sequestration of lymphatic tissue derived from portions of the primitive sacs during embryonic life [9]. They commonly occur in head and neck, but may also be seen in mediastinum, axilla, inguinal and retroperitoneal region. They occur with equal occurrences in males and females with 50—65% present at birth and 80—90% detected before the end of second year of life [10]. Lymphangiomas are
soft, cystic and usually transilluminant. In head and neck they most commonly occur in the posterior triangle of the neck and may suddenly increase in size with infections or haemorrhage and may be misdiagnosed as a branchial cleft cyst or a lipoma.

Some authors have used the terms lymphangioma and cystic hygroma interchangeably. These lesions

Fig. 3 Two weeks after third injection.

Fig. 4 Two weeks after fifth injection.
are benign but cause significant morbidity due to their large size and can have an overall mortality rate of 3.4—5.7% [11,12]. The diagnosis of congenital vascular malformation and cystic hygroma can be established by clinical assessment and radiology using CT scan and magnetic resonance imaging.

Most reports on the treatment of congenital vascular malformation and cystic hygroma are centred around surgical excision of these lesions either for achieving cosmesis or for relieving pressure effects. The results of surgical excisions are not very encouraging in those cystic hygromas that are large in size. Due to extensive ramifications, the excision becomes tedious and difficult if the sheets of tissue extend between major vessels and nerves. For this reason the nerve palsies and recurrences are common post-operatively. In order to circumvent the morbidity and mortality following surgery of extensive lesions, injection of variety of sclerosing agents have been experimented as an alternative treatment. We attempted intralesional injection of bleomycin to produce sclerosis and reduce the size of swelling. Very few studies in the past have made use of bleomycin as a sclerosing agent for this condition. With this therapy we encountered no major complication and there was no mortality. The rate of residual disease was 70% in our cases. The surgical excision carried out later in three such cases for their residual disease was not fraught with any difficulty. Considering the level of response achieved with this modality of treatment we cannot rule out a mechanism of action other than the sclerosing effect of this drug.

Umezawa first developed bleomycin as an anti-tumor agent in 1966 and its mechanism of action was by inhibition of DNA synthesis [13]. But later, this drug was also known to produce a sclerosing effect on the endothelial cells with non-specific inflammatory reaction. In 1977, Yura et al. first used it as a sclerosing agent in lymphangiomas [1]. For better confinement of this drug, it was used in the form of microsphere in oil emulsion by Tanigawa in 1987 and was injected into aspirated cyst cavities in cystic hygroma [14]. The side effects of bleomycin sclerotherapy are minimal except for local swelling and inflammation. The most feared complication of the use of this drug is pulmonary fibrosis reported when it is administered during cancer therapy. For sclerotherapy in cystic hygroma Sung et al suggested the dose of less than 1 mg/kg at an interval of not less than 2 weeks, with the total dose limited to 5 mg/kg [15]. We used similar regime and injected the solution in concentration of 1 mg/ml for larger lesions and 2 mg/ml for smaller lesions with the maximum dose limited to less than 6 mg/kg. By coincidence our study was carried out at nearly the same time as

<table>
<thead>
<tr>
<th>Authors and year of publication</th>
<th>Number of cases</th>
<th>Period of study</th>
<th>Site</th>
<th>Treatment</th>
<th>Complications</th>
<th>Residual/recurrence (%)</th>
<th>Operative mortality</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emery et al. (1984) [10]</td>
<td>37</td>
<td>1962–1982</td>
<td>Cervico-facial</td>
<td>Excision in 34 cases</td>
<td>Nerve palsies—33%</td>
<td>32</td>
<td>52</td>
<td>Not reported</td>
</tr>
<tr>
<td>Kennedy et al. (2001) [18]</td>
<td>46</td>
<td>1998–2000</td>
<td>Cervico-facial</td>
<td>Excision in 34 cases</td>
<td>Nerve palsies, bleeding</td>
<td>35.2 (12 cases)</td>
<td>50</td>
<td>Nil</td>
</tr>
<tr>
<td>Charabi et al. (2000) [19]</td>
<td>44</td>
<td>1962–1997</td>
<td>Cervico-facial, hypopharynx, and larynx</td>
<td>Excision</td>
<td>Nerve palsies, impaired respiration, speech pathology, dysphagia</td>
<td>44%</td>
<td>25</td>
<td>12.5%</td>
</tr>
</tbody>
</table>

Table 2. Results of surgical excision in cystic hygroma of head and neck region in some published series.
the study by Sanlialp et al., which was published in 2003. Our results with the use of bleomycin in lymphangiomas are quite similar to theirs [16]. However our study also includes use of bleomycin in haemodynamically less active congenital vascular malformations.

Bleomycin is absorbed systemically even when used as a sclerosing agent as reported by Siegel. This was observed when it was administered intrapleurally for a malignant pleural effusion in a case with breast cancer [17]. In patients whose creatinine clearance is less than 25–35 ml/min, the half-life of this drug would increase exponentially and as this drug is not dialyzable it would produce systemic toxicity.

Results in the few published series of the surgical excision of the head and neck cystic hygroma suggest that complications of surgery in such cases vary between 12.5 and 44% with the most common complication being nerve palsies (Table 2). The rate of residual disease or recurrence with surgical excision could vary from 25 to 52% and the mortality is reported to be between 0 and 20.8% [10,18–20]. Besides, a surgery can also produce a bad scar. In the study conducted by Charabi et al. 36% patients complained about cosmesis postoperatively [19].

Although our results with bleomycin sclerotherapy show a higher incidence of residual disease yet they score over the surgical results by not producing any scars or complications. Encouraged by the response with intralesional injection of bleomycin in these 10 cases of congenital lymphatic and haemodynamically less active vascular malformations we now favour bleomycin sclerotherapy before considering surgical excision in all such cases in our hospital.

References