ORIGINAL ARTICLE

Intralesional Injection of OK-432 in Cystic Hygroma

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ABSTRACT

Background: Lymphangiomas are congenital malformations of the lymphatic system with characteristic dilated endothelium-lined spaces. It is vulnerability to infection or chemical irritants cause spontaneous reduction in size and in some cases complete resolution. Intralesional injection of OK-432 or Picibanil (lyophilized incubation mixture of Group A Streptococcus pyogenes of human origin) is slowly gaining recognition as its safety and efficacy standards have shown to avoid complications resulting from surgical interventions. The objective of this study was to evaluate the clinical outcomes of cystic hygroma patients who received OK-432 injections.

Methods: In between 2011 and 2013, six patients with cystic hygroma received intralesional injection of OK-432. All the patients were assessed clinically and radiologically either via ultrasound, computer tomography (CT) or magnetic resonant imaging (MRI) prior to and after receiving the injections. Patients' response towards treatment was classified as total shrinkage, marked shrinkage (greater than 50% reduction in size), slight shrinkage (less than 50% reduction in size) or non-responsive to treatment.

Results: Mean duration of follow-up was 12 months. Total shrinkage was achieved in one patient, marked shrinkage in three patients and one patient experienced mild shrinkage. Only one out of the six patients showed no response to treatment. None of the patients in this study experienced serious complications or adverse effects post intralesional injection of OK-432.

Conclusions:
Intralesional OK-432 injection is an effective and safe alternative in treating cystic hygroma.

KEY WORDS:
Cystic Hygroma, Lymphangioma, OK-432, Picibanil

INTRODUCTION

Lymphangiomas consists of various sizes of lymphatic channels and cystic spaces ranging from microscopic channels (cavernous lymphangioma) to large cysts (cystic hygroma).[1] As these lesions enlarge; usually due to haemorrhage or infection, it causes cosmetic deformity and compression to adjacent local structures such as the airway and the surrounding vessels.[2]

Surgical excision has in the past been a popular therapeutic option for such malformations. However, it's high rate of recurrence as a result of incomplete excision and other associated complications such as facial nerve paralysis, haematoma. Frey's syndrome and scarring has no doubt made it a less favourable option in present times.[3]

Therefore, non-surgical alternatives such as intralesional injection of sclerosing agents have become an accepted alternative in reducing morbidity whilst effectively treating the lesion.

OK-432 or Picibanil, is a sclerosing agent derived from a low virulence strain of Streptococcus pyogenes incubated with penicillin. It stimulates an inflammatory response that causes local inflammation resulting in regression of the lesion.[4]

The purpose of this study was to evaluate the clinical outcomes of cystic hygroma patients who received OK-432 injections.

MATERIALS AND METHODS

A retrospective review of six patients diagnosed with cystic hygroma and treated with OK-432 was carried out from 2011 to 2013 at the Otorhinolaryngology Department, Sarawak General Hospital (Table I).

The study sample comprised of two males and four females, age; ranged from one month to 49 years old (mean age was 15 years). All the patients underwent physical examinations, fine needle aspiration of the primary site and imaging either via ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI), with documentations of the site and dimensions of the swellings. None of the patients received surgery, alcohol sclerotherapy or systemic corticosteroids prior to the administration of the intralesional OK 432 injections.

The intracystic fluid of the cystic hygroma was first aspirated, followed by injection of OK-432 (concentration, 0.01 mg/mL) with ultrasound guidance. The total number of injections performed was eight, with two patients who received more than one injection.

Post OK432 injection, all six patients underwent clinical examination and clinical photography to document the progress of the swellings. Patients' own subjective statement with regards to the size of the lesion post injection was also documented.

This article was accepted:
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Table I: Demographics of the subjects included in this study

Patient #	Gender	Race	Age first presented	Site	Dimension (cm)
1	Female	Pakistani	4 yr	Left neck	3.0 x 1.3 x 2.6
2	Male	Malay	18 yr	Right neck	2.0 x 6.0 x 7.0
3	Female	Chinese	6 yr	Left neck	3.4 x 3.2 x 2.3
4	Male	Malay	1 mth	Left axillary	3.8 x 1.9 x 2.9
5	Female	Malay	15 yr	Left neck	*No documentation available
6	Female	Bidayuh	49 yr	Right neck	8.5 x 5.6 x 9.5

Table II: Outcome after treatment with OK-432 and total number of treatment sessions for each patient

Patient No.	No. of sessions with OK-432	Aspirate	Duration of follow up	Overall outcome
1	1	20mL of hemoserous fluid aspirated. 5mL of OK-432 injected.	6 months	No response
2	2	1st session: 20mL of straw-coloured fluid aspirated. 10mL of OK-432 injected. 2nd session: 15mL of serous fluid aspirated. 6mL of OK-432 injected.	12 months	Total shrinkage
3	2	1st session: 5mL of hemoserous fluid aspirated 5mL of OK-432 injected 2nd session: 25mL of brownish fluid aspirated. 10mL of OK-432 injected.	6 months	Marked shrinkage
4	1	10mL of hemoserous fluid aspirated. 5mL of OK-432 injected.	6 months	Marked shrinkage
5	1	20mL of serous fluid aspirated. 5mL of OK-432 injected.	4 months	Mild shrinkage
6	1	60mL of serous fluid aspirated. 5mL of OK-432 injected.	4 months	Marked shrinkage

All the findings were tabulated and classified as follows; total shrinkage, marked shrinkage (more than 50% reduction of lesion size), slight shrinkage (less than 50% reduction of lesion size) or no response.

RESULTS

Post OK-432 injection, total shrinkage of lesion was achieved in one patient, marked shrinkage in three patients and mild shrinkage in one patient. Only one patient did not respond to the treatment (Table II).

Out of the four patients who achieved good response (total or marked shrinkage) towards OK-432 injection, two patients responded with a single injection whereby another two patients required a second injection.

Post OK-432 injection, four patients developed fever. An 18 years old gentleman developed high grade fever (T○C 40) requiring a one week course of antibiotic. The remaining three patients experienced transient pyrexia which resolved overnight. There were no other serious complications observed.

DISCUSSION

In a 1994 case study, Ogita et al. described 64 children, in whom 38 (59%) children achieved marked or total shrinkage after OK-432 injection.[5] Subsequent publications by Hall et al. in 2003 reported total or marked shrinkage in 7 (37%) out of 19 patients tested.[6] In our case series, we observed a clinical curative effect in treating cystic hygroma with OK-432 injection. Overall, four out of six had total or marked shrinkage. None of the patients in this study underwent surgical excision. The remaining patients within the group which did not achieve total shrinkage remain under our follow up, with plans of future courses of OK- 432 injection.

In our setup, parents were reluctant to allow their children to undergo repeated injections when there had been little or no response after the initial injection was given. Furthermore, the limited supply of OK-432 in our centre hindered subsequent injections to our patients as there was always a long waiting period involved in the logistics of transporting the sclerosant from Japan.

Hall et al and Ogita et al. reported the maximum number of injections received by each child in their studies were 5 injections and 16 injections respectively.[6,7] Nonetheless, systematic reviews of literature on lymphangioma patients receiving OK-432 therapy reported a mean number of two injections per patient.[8,9] These group of patients had an overall response rate ranging from 50% to 95%, with complete remission occurring in 28 to 57% of cases.[8]

To date, there is no fixed guideline or algorithm, which specifically quantify the maximum number of injections needed and the duration between each injection. Often times, the number and duration between injections are adjusted based on the response rate of each individual.

Yoo et al., reported a response rate to repeated injections at 83% with an interval injection period of two weeks to three months, with a mean number of injections at two. Non-responders to OK-432 were given repeated injections up to three times, after which, second line treatment was sought. This study highlighted macrocystic lymphangiomas and those located below the myolohyoid muscle had a more favourable outcome to OK-432.[10] Similar findings were reported in the Starship Children's Hospital series of seven

patients, who received between four to seven injections per patient. Favourable outcome was again evident in the macrocystic lymphangioma group which showed faster resolution and required the least number of repeated injections.[11]

There were no serious adverse effects after OK-432 injection observed in our study. Documented complications of OK-432 injection were highlighted by Hall et al.; whereby one child developed an abscess at the injection site that required incision and drainage and another child developed stridor as a result of partial tracheal obstruction.[6]

There are several potential advantages of OK-432 injection in comparison to surgical excision. OK-432, being minimally invasive, could reduce surgical related neurovascular injuries and unsightly surgical scars which may lead to body image issues. Furthermore failure of OK-432 treatment did not interfere with subsequent surgical removal of the lesion.[6]

Our series of six cases showed intralesional injection of OK-432 provides a simple, safe and reliable alternative treatment for cystic hygroma. Despite an outcome that was uniformly positive and without serious or permanent side effects, it is emphasised that this should not be a general statement accorded to all cystic hygroma cases treated with OK432. Statistical analysis was not required in our series as there was no comparison with the standard treatment.

Proper documentation guidelines may be able to aid the clinician in identifying the good responders to OK-432. Pre and post treatment assessment documentation should include lymphagioma predominant types (macrocystic, microcystic or mixed), patient demographics, location of lymphangioma, types of functional impairment, number of injections and duration between each injections.[12] Therefore future studies employing the use of a standard interventional comparison, which will be necessary if the intervention is to be quantified, together with larger number of cases, will be able to raise its value to a control trial.

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