

OK-432: An effective sclerosing agent for the treatment of lymphangiomas of head and neck

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Abstract

Objective: The basic objective of this study was to find out the efficacy of OK-432 for the conservative treatment of lymphangiomas of head and neck regions at the *Department of ENT-Head & Neck Surgery of Tribhuvan University Teaching Hospital (TUTH), Kathmandu, Nepal.*

Methods: It was a hospital based prospective, cross-sectional, case series, conducted among the patients suffering from different lymphangiomas of head and neck regions and treated with intra-lesional injection of OK-432, from March, 2005 to September 2006. Altogether eleven patients were enrolled in this modality of treatment out of which one patient was excluded from the study, which was treated surgically due to very ugly scar at the site of lesion resulting from previous surgery for the same. The data were analyzed by using simple mathematical tools like percentage and frequency.

Results: Out of ten patients treated with intralesional injection of OK-432, absolute response, i.e. total resolution of swelling was found in nine patients (90%) after the first dose. Remaining one patient also responded well on the treatment but some residual swelling was in situ for which second dose was given. After the second dose it was also totally resolved. In this way we achieved 100% response after the second dose of OK-432.

Conclusion: The results of this study so far indicate that OK-432 is an effective and safe tool for the treatment of lymphangioma of head and neck region. As the procedure can be done in an out patient department, without hospitalization and has got minimal side effects, it can be proposed as the first line treatment of lymphangiomas of head and neck.

Key words: *Lymphangioma, OK-432, Sclerotherapy, Sclerosing agent, Head and Neck.*

Lymphangioma are rare congenital malformation of lymphatic system. The neck is the most common site 25% of all cases.¹ Localized cystic lesions are more inclined to occur in the neck where as diffuse involvement of the lower third of the face is much more common.² Majority, 50-60% recognized at birth and 80-90% are evident by the end of the second year of life, corresponding the period of greater lymphatic growth.³ Lymphangiomas have been classified into three groups: lymphangioma simplex, cavernous lymphangioma and cystic hygroma.

Lymphangiomas are benign, slow growing tumour having a tendency to grow in an infiltrating manner into the surrounding tissues leading to compression, resulting functional disturbances.⁴ Clinically they have doughy feel, pitting oedema, and does not empty with compression. Most of the time diagnosis is made on the basis of history, clinical findings and confirmed by cytopathologically or histopathologically. Imaging technique identifies the

extension of the tumour but they do not enhance with gadolinium.

Sudden increment of the size of the tumour usually signifies either infection or haemorrhage. Rarely the disease may regress spontaneously. Treatment may be necessary if they become symptomatic functionally or cosmetically. The most accepted treatment is still surgical excision. However, when it infiltrates vital neurovascular neck structures, complete excision is difficult and if only partial, the recurrence rate is very high as well as high risk of surgical complications.⁵

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The most frequently used alternative treatment is to inject sclerosants into the lesion. Here we used OK-432 (Picibanil) as a sclerosing agent for the treatment of lymphangiomas of head and neck. The basic objective of this study is to assess the efficacy of OK-432 sclerotherapy in head and neck lymphangiomas.

OK-432 (Picibanil) is a lyophilized incubation mixture of group A Streptococcus Pyogenes of human origin.⁶ It has lost its streptolysin producing ability but retained the abilities that produce local inflammatory mediators. At the site of injection, due to the effect of various inflammatory mediators, the permeability of endothelial cells of lymphangioma vessels will increase, and thus accelerate lymph drainage and increase high flow, let to shrinkage of the cystic spaces.⁶ The main advantage of this agent is there is no evidence of fibrosis around the cyst,⁵ so even in cases of failure; surgery will be not complicated by fibrosis. The complications of OK-432 include partial tracheal obstruction, local oedema, fever, local inflammatory response and rarely abscess formation.⁵ But local inflammatory reaction does not cause any damage to the overlying skin and does not lead to scar formation.⁷

Materials and methods

All clinically suspected cases of lymphangioma, attending to *OPD of ENT-Head and Neck Surgery of TU Teaching Hospital, Kathmandu, Nepal* from March, 2005 to September, 2006 were referred to the authors, who were further evaluated clinically after complete history taking and demographic recording. During clinical evaluation emphasis was given to the site involved and extension into the surrounding structures. Doughtful cases were further evaluated radiologically and or imaging (CT/MRI) and confirmed their extent. Further they were advised for FNAC for the cytopathological confirmation.

Only those cytopathologically confirmed cases whose extension was limited to head and neck and upper thoraco-axillary regions were subjected to this modality of treatment. Altogether eleven patients were enrolled for this modality of treatment but one patient was excluded from the study that was treated surgically as he had very ugly scar in cervicofacial region due to previous surgery for the same and patient wanted to remove his scar along with the disease. So finally only ten patients were enrolled for the study.

We used OK-432 (*picibanil: Chugai pharmaceuticals co ltd. Tokyo; courtesy: Prof. Ogita S, Children's research Hospital Kyoto-Japan*) as a sclerosing agent for the sclerotherapy of all these enrolled cases. The medication OK-432 (0.1 mg vial) was diluted with

10ml of normal saline and prepared for the injection. The most bulging site was chosen for the aspiration and maximum volume of fluid from the lymphangioma was aspirated. The needle was kept in situ and exactly same amount of diluted OK-432 was immediately injected. This procedure was done in out patient department and not a single case required hospitalization. The second dose was given six weeks after if needed. In all patients the amount of fluid aspirated from the lesion and intralesional injection of OK-432 was variable ranging from 5ml to 39ml maximum. All patients were advised for follow up at the interval of six weeks and in first follow up, in nine patients, previous swelling was totally disappeared. Only one patient needed second dose of therapy as it had some residual swelling even after six weeks. But after second dose of sclerotherapy the residual swelling was totally disappeared. No recurrence was noted till date (*median follow up=14 months*). All parameters (variables), like the amount of fluid aspirated from the lesion and intralesional fluid injection, site, size and extent of the swelling before and after sclerotherapy, complications developed if any were recorded. These parameters (variables) were analyzed by using simple mathematical tools like percentage and frequency. The results were derived and conclusions were made on their basis.

Results

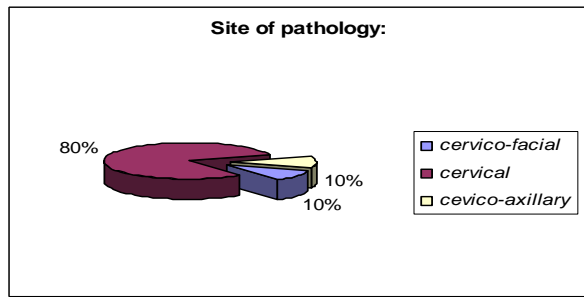
The patient's cohort included ten patients having seven male and three females, ranging in age 18 months to 25 years (nine patients were below the age of six years). Cervical pathology was found to be the commonest pathological site among all that is shown in Fig. no 1.

As mentioned earlier, OK-432 was injected into the lesion, to the equal amount of fluid that was aspirated from the lymphangioma. The amount of sclerosant that was injected into the lesion (minimum 5ml and maximum 39 ml) was shown in fig. no 2.

After injection of sclerosants, every patient was followed up at the interval of six weeks and the size of the swelling was reassessed. It was found that in the first follow up, the swellings of nine patients out of ten were totally disappeared where as in one patient's it was reduced but residual swelling was there which was disappeared after the injection of second dose of sclerosant, that is shown in Fig. no 3.

After the injection of sclerosant, in each patient, we also assess the complications encountered if any and following minor complications were noted during entire therapy that is shown in Fig. no 4:

Fig. 1: Site of Pathology



Site: Cervico-axillary



Site: Cervical

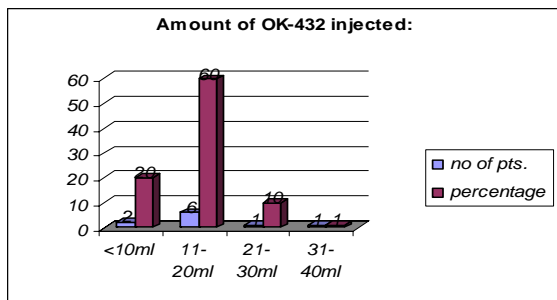


Fig. no 2: Amount of sclerosant injected:

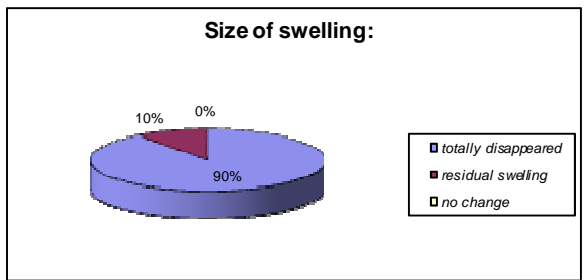


Fig. no 3; size of the swelling after six weeks (1st follow up):

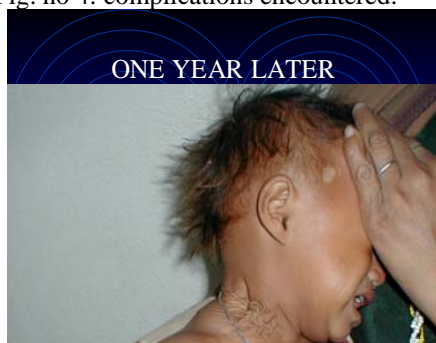


Prior to OK-432 sclerotherapy

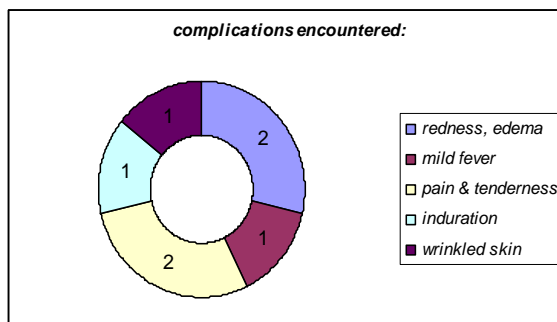


After six weeks of sclerotherapy

Fig. no 4: complications encountered:



Wrinkled skin at the site of lesion



Discussion

Although surgery is the treatment of choice for the lymphangiomas, the risk of complications, incomplete excision and recurrence of the disease compelled clinicians need to develop alternative treatment modality for the disease and development of sclerotherapy with OK-432 is the consequence of this need. In our case series of ten patients, we found very optimistic results, absolute response in 90% after first dose and in 100% after second dose; which also compelled us to continue this modality of treatment with larger sample size to make the final conclusion. Luzzatto et al⁸ had treated 29 children of lymphangioma with OK-432 in Padua, Italy and made conclusion that OK-432 sclerotherapy remained their first line therapy for lymphangiomas, avoiding surgery in most cases.

Similarly Alonso et al⁵ reported a case of cervical lymphangioma treated with OK-432 and found that it was totally remitted within a month and no recurrence was noted till 16 months of sclerotherapy. Likewise Bloom et al⁹ had done a study in USA for the management of lymphatic malformation with the sclerotherapy of OK-432 and made conclusion that it is effective for macrocystic lymphatic malformation but less effective for microcystic and mixed lesions as well as lesions outside the head and neck regions.

Wheeler et al¹⁰ had done a similar study in Newzeland, on seven children under the age of five years suffered from lymphangiomas, who underwent OK-432 sclerotherapy as day case procedures and on the basis of its response, made a conclusion that OK-432 appears to be safe and

effective treatment for the macrocystic component of lymphatic malformation.

Likewise Baniueghbal B and Davies MR¹¹ conducted a similar study in South Africa on 35 patients suffered from lymphangioma and treated with OK-432 sclerotherapy and found complete regression in 96% cases. Similarly Rautio et al¹² also conducted a similar study on 14 children of lymphangioma of age 14 months to 42 years in Finland, to assess the efficacy of OK-432 sclerotherapy and observed that treatment of lymphangioma with this modality was safe and effective.

At the same time Giguere et al¹³ conducted a prospective multi-institutional trial therapy of lymphangioma with OK-432 in USA on 29 patients (age: six months to 18 years) suffering from lymphangioma of head and neck regions and observed very successful outcome i.e. effective in 86%. Claesson G and Kuylenstierna R¹⁴ carried out a prospective study in Sweden in 32 patients (28 children) of lymphangioma and treated with intralesional injection of OK-432 and found excellent results without any serious adverse effects. They made conclusion that OK-432 is effective and is proposed to be the first line of treatment for lymphangioma.

Laranne et al¹⁵ had treated 11 children of lymphangioma of head and neck in Finland with intralesional injection of OK-432 and found excellent results. They made conclusion that OK-432 sclerotherapy is safe and effective therapy as a first line of treatment for lymphangioma.

Similarly Charabli et al¹⁶ treated 44 patients of lymphangioma surgically and analyzed their long-term results, which lead the authors to search for a new therapeutic modality. As a result they treated two patients of cystic hygroma with intralesional injection of OK-432 and found total regression of disease.

Luzzatto et al⁸ conducted a study in Italy for the treatment of lymphangioma with OK-432 on 15 patients, age ranging from birth to 15 years at the interval of seven years and as per the results obtained they recommended that OK-432 is proposed as a first line option for the treatment of lymphangiomas.

Regarding side effects of OK-432, we observed minor side effects like mild oedema, redness, fever lasting one to three days, pain, indurations and wrinkled skin at the site of injection during the entire treatment course. Similarly Schmidt B, Schimpl G, Hollwarth ME¹⁷ also treated eleven children suffering from lymphangioma in Austria with OK-432 and found good response without any complications except fever lasting 2-3 days and slight tenderness with swelling of the lymphangioma.

Likewise, Ogita et al⁶ treated 64 lymphangiomas with OK-432. The only side effects they found were fever, lasting 2-4 days and local inflammatory reaction of 3-7 days duration. In contrast, Sichel et al¹⁸ treated 11 patients of cervical lymphangioma in Israel with OK-432 and observed no complication at all during the entire course of therapy.

Conclusions

The results of this study so far indicate that OK-432 is an effective and safe tool for the treatment of lymphangioma of head and neck region. As the procedure can be performed in an out patient department, without hospitalization and has got minimal adverse effects, it can be proposed as the first line treatment of lymphangiomas of head and neck.

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