RESEARCH ARTICLE

Treatment of Excision Wound of Melanoma In Situ of the Trunk and Extremities with Zinc Chloride Solution

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Conflict
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Abstract

The majority of physicians treating melanoma in situ recommend a 5mm to 1cm margin with excision into the subcutaneous tissue extending between the superficial and the deep fat. There is always the potential for an unrecognized invasive component in a melanoma in situ, making aqueous zinc chloride solution an ideal agent to treat the excision wound of a melanoma in situ of the trunk and extremities. Zinc chloride solution penetrates deeply and widely, killing and fixing tissue when applied to the excision wound, facilitating the excision by allowing for a simple saucerized excision with a narrower and thinner margin while ensuring the treatment of any possible unrecognized invasive components. Zinc chloride has been used in a paste since 1835 to treat skin cancers and melanoma but unlike pastes zinc chloride in solution is recognized by the U.S. Food & Drug Administration as a generally safe substance (Code of Federal Regulations Title 21 [Part 182]). The solution penetrates as deeply and widely and effectively as in the paste which Mohs described to be an inactive vehicle for the active ingredient, zinc chloride solution. Mohs reported a large significant survival benefit (p=0.003) for invasive melanoma using surgery combined with zinc chloride over conventional melanoma surgery. Zinc chloride solution without the paste is a new medicine effective as a surgical adjuvant in the treatment of the excision wound of a melanoma in situ of the trunk and extremities. Zinc chloride can be used as a surgical adjuvant for any melanoma, but melanoma in situ of the trunk and extremities is the logical starting point for a physician interested in using this adjuvant in the treatment of melanoma. Zinc chloride is very powerful and potentially scarring and should be used on the excision wound of a previously histologically diagnosed melanoma only.

Introduction

Mohs, the founder of the American College of Mohs Surgery and inventor of Mohs surgery, believed that surgery can spread a melanoma and to prevent this he used a combined technique of surgery and zinc chloride which he termed chemosurgery. In the Mohs technique the active ingredient, aqueous zinc chloride solution, is applied to the melanoma suspended in a paste. Historically, zinc chloride has been used suspended in a paste since 1835, but paste in modern melanoma surgery is not recognized by the FDA as a generally safe substance. Pastes containing zinc chloride have been stigmatized by improper lay usage, and many in the American College of Mohs Surgery feel that pastes are an awkward vestige of the past. The FDA recognizes aqueous zinc chloride solution as a generally safe substance (Code of Federal Regulations Title 21 [Part 182]), and has approved aqueous zinc chloride solution for intravenous use in low concentration. A statistical analysis of data from two historically recognized melanoma surgical series is presented showing a large significant survival improvement (p=0.003) with zinc chloride. A discussion of the mechanism of action of aqueous zinc chloride solution in protecting against metastases is provided to give a rationale for the use of zinc chloride. Aqueous zinc chloride solution is a new medicine for use in the treatment of melanoma.

This paper introduces an effective technique using aqueous zinc chloride solution which allows for a more conservative excision margin than conventional surgery for melanoma in situ of the trunk and extremities. [1,2] The treatment of facial lesions with zinc chloride is more difficult, potentially scarring, and lesions near the eye must be avoided. As a general rule the author has treated facial melanoma in situ with fresh-tissue surgery using a deep saucerized shave excision technique and has also utilized curettage at the very outer margins of the in situ melanoma. Traditionally a 50% zinc chloride solution concentration has been used to treat melanoma and melanoma in situ. The author uses a 50% concentration but has experimented with a 20% solution (similar to the commonly used astringent 20% aluminum chloride) and found that it is less powerful but still acts to kill and fix tissue (i.e. preserves the microscopic integrity of the killed tissue). Even at a 20% concentration zinc chloride is powerful and must be used only on the excision wound of a previously diagnosed melanoma. A technique using 50% zinc chloride solution is presented for melanoma and melanoma in situ.

Methods

Technique for Melanoma and Melanoma In Situ

Immediately following a conservative saucerized excision of a previously histologically diagnosed melanoma or melanoma in situ, 50% zinc chloride solution is applied in a dose which may vary from a single brief Q-tip application for a small facial melanoma in situ to 2 x 2 sterile gauze saturated with solution manually applied and held briefly in place depending on the size, location, and thickness of the excised lesion. Deep penetration occurs instantly, and mild pressure may be used to obtain hemostasis. Absorbable sutures may be used for hemostasis if necessary. Control of bleeding while applying zinc chloride solution to the excision wound is a unique feature of the technique which the author has found sterile gauze to be most effective. The zinc chloride is first applied with sterile gauze containing the zinc chloride solution, then replaced with dry sterile gauze taped over the treated wound as a pressure dressing which effectively stops the bleeding. The dressing is left in place and the patient advised to soak off the sterile gauze with water (as in showering) the next day and then redress.

The greater the amount of solution applied, the deeper and wider the penetration of zinc chloride. A smaller and thinner excision margin can thus effectively be removed prior to the zinc chloride treatment. A single conservative circular saucerized excision with a narrow peripheral margin and deeper in the center can clear most melanomas and provides an ideal surface for the application of the zinc chloride solution. Permanent or frozen section histology may be used to confirm that a tumor-free excision has been achieved. If positive margins are found a tangential re-excision of the area of residual tumor may be performed. The author has rarely found a re-excision to be necessary. The excision can be mapped as in a Mohs surgery to localize any possible residual tumor. The wounds heal by secondary intention, although a repair can be performed. See Figures 1-3.

Fig. 1: Melanoma in situ of the left posterior shoulder in a 78 year old male.

Fig. 2: Conservative excision. The melanoma in situ was removed with a fresh-tissue conservative saucerized excision. Shown is the excision wound.

Fig. 3: Treated excision wound. Immediately following the conservative fresh-tissue excision 50% zinc chloride solution was applied with a saturated 2x2 gauze held manually briefly in place with mild pressure. Absorbable sutures were not required for hemostasis. The wound healed by secondary intention, although a repair can be performed.

Limitations

Zinc chloride solution penetrates deeply and widely and should be applied only to the excision wound of a previously histologically diagnosed melanoma or melanoma in situ. Zinc chloride should not be applied to a wound based on a clinical diagnosis only such as a simple excision or biopsy wound. The eye is very sensitive to zinc chloride and lesions on or near the eyelids should not be treated. Cartilage is also sensitive to the action of zinc chloride and the solution should not be applied directly on the cartilage ofthe nose or ear. Caution is used if applying over a major artery or nerve.

Formulation

Aqueous zinc chloride has historically been used suspended in a paste. Mohs described the paste to be an inactive vehicle for suspension of the active ingredient, aqueous zinc chloride.[3,4] Zinc chloride is available as zinc chloride granular USP, and a solution is prepared by dissolving zinc chloride in distilled water. A saturated solution is prepared by dissolving four parts of zinc chloride to one part of distilled water by weight. A formulation of 50% zinc chloride can be made by mixing 80g zinc chloride with 70g distilled water. This formulation was derived by diluting a saturated solution. A chloride ion electrode analysis of the 80g to 70g formulation revealed a 54.8% zinc chloride weight percent. A more traditional alternative method of making a 50% zinc chloride solution is to dissolve 50g of zinc chloride granular USP in 100ml of distilled water, as 1ml of water weighs 1g. A physician new to the use of zinc chloride may want to begin by using this weaker concentration. When preparing a zinc chloride solution, oxychlorides may form resulting in a cloudy solution. In a 100ml solution drops of 5% distilled aqueous acetic acid solution or drops of a dilute hydrochloric acid solution can be added to dissolve the oxychlorides and create a clear zinc chloride solution.

Surgery with Zinc Chloride vs. Conventional Surgery for Melanoma

A statistical analysis of Mohs data consisting of 103 consecutive cases of mostly advanced melanomas with 20% presurgical lymph node metastases treated between 1937 and 1968 with zinc chloride was performed at the UCLA Department of Computational Medicine.[3,5,6] These 103 cases were quantitatively compared for survival by depth of invasion to a series of 162 primary melanoma cases treated with conventional surgery at the Massachusetts General Hospital. These cases at the Massachusetts General Hospital became the foundation for Clark's melanoma survival by level of invasion.[7] In the zinc chloride series, 86 of 103 had at least five years follow up. All cases in the Massachusetts General series had at least five years follow up. The analysis showed a statistically significant 53% improvement in overall survival rate ($p=0.003$; HR = 0.53) for the zinc chloride treated melanomas. The poor prognosis of the 20% metastatic lesions was not factored into the analysis. The quantitative comparison of five-year survival by depth of melanoma invasion was computed by integrating the differential rates of survival by depth in the two studies (thin level II to deep level V). Surgery with zinc chloride had a five year 53% survival rate improvement vs. conventional surgery despite 20% metastatic disease.

In the Mohs zinc chloride series there were 4 five-year determinate cases of level II, with a survival rate 100%, 13 five-year determinate cases of level III, with a survival rate 92.3%, 14 five-year determinate cases of level IV, with survival rate 64.3%, and 55 five-year determinate cases of level V invading into the subcutaneous fat with the poorest prognosis, survival rate 32.7%. There were 162 cases in the Clark series, all primary melanomas stratified by depth of invasion with 29 cases of level II, five-year survival rate 90.0%, 58 level

III, five-year survival rate 57.0%, 59 level IV, five-year survival rate 40.7%, and 16 level V invading into the subcutaneous fat, five-year survival rate 18.8%.

In addition to the Mohs data, nine physicians, including the author, contributed to a melanoma registry of 179 cases between 1981 and 1991. In 64 five-year determinate cases of thin melanomas (<0.85mm) survival was improved by 60% using a simplified treatment with zinc chloride applied to the melanoma excision wound compared to conventional surgery. There was a 95.7% five-year survival with zinc chloride applied to the excision wound vs. 88.9% five-year survival with conventional fresh-tissue excision only, hazard ratio 0.37.[8,9] There were not enough patients in the registry to make definitive statistical determinations. For the thin melanomas, a sample size of 240 per group is needed. In the Mohs technique the excision wound is treated after a layer-by-layer removal.

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Discussion

The Mohs data of the 103 consecutive cases treated topically is old taking 30 years to complete between 1937 to 1968. Paradoxically, the timing of this study makes the data more persuasive and decisive. The study was completed during a period of time when advanced and metastatic cases were commonly seen prior to surgery. The zinc chloride melanoma statistical finding of a 53% significant (p=0.003) overall five-year treatment survival improvement despite the presence of metastatic disease in 20% of the cases vs. all primary melanomas, decisively shows a benefit for the use of zinc chloride as a perioperative topical treatment.

The remarkable benefit of a large significant survival improvement despite the presence of metastatic disease in 20% of the cases can be explained by the fixative property of zinc chloride. Zinc chloride may stimulate immunity against perioperative tumor growth.

This tumor growth is a phenomenon of increased circulating cancer cells, decreased tumor immunity, and increased potential for metastases occurring at the time of surgery.[10-28] According to reference [10], surgery is a trigger for metastases. When applied to an excision wound of a melanoma zinc chloride penetrates deeply and widely beyond the surgical margins into the tissues and surrounding lymphatics, not only killing but also fixing any possible occult malignant cells that may play a role in the phenomenon of perioperative tumor growth. The fixing of melanoma cells, that may be present at the surgical margins and lymphatics, detectable only by molecular staging regardless of the size of the excision, has been shown in experimental studies to stimulate immunity against metastases of melanoma.[29,30]

Conclusion

Historically, the active ingredient, aqueous zinc chloride solution, has been used in a paste since 1835, but unlike paste, zinc chloride in aqueous solution is recognized by the U.S. Food & Drug Administration as a generally safe substance when used in accordance with good manufacturing practice (Code of Federal Regulations Title 21 [Part 182]). Aqueous zinc chloride solution has been approved by the FDA for intravenous use in low concentration. The technique presented using aqueous zinc chloride solution in proper dosage applied to the excision wound of a previously diagnosed melanoma in situ of the trunk and extremities is safe and effective. The effectiveness of zinc chloride for the treatment of melanoma in situ is substantiated by the statistical findings and the potential for surgery alone to be a trigger

for metastases as previously discussed. The finding that surgery with zinc chloride had a five-year 53% survival rate improvement vs. conventional surgery despite 20% metastatic disease indicates the mechanism of action of zinc chloride is to protect against perioperative tumor growth.

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