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Dramatic Response of Topical Doxycycline in Umbilical Granuloma: Report of 84 Cases

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Abstract

We previously observed that topical doxycycline powder was effective in the treatment of umbilical granuloma. This study aims to evaluate the efficacy of this agent. The patients were randomly assigned into inpatient group and outpatient group. Doxycycline powder was administered topically once daily for 5 days. The protocol was restarted if no response observed. Eighty-four patients were included in this study. With one course of therapy, the overall cure rate was 82.14% (69/84), and the statistical difference in response rate was not significant between the 2 groups ($P > .05$). With 2 courses of therapy, the overall cure rate was 94.05% (79/84). No complication was observed during treatment. No recurrence was observed during follow-up. The treatment of umbilical granuloma using topical doxycycline is safe and efficacious. The administration of the agent can be performed conveniently by parents at home. This protocol could be considered to be the first treatment option for this disorder in neonates and infants.

Keywords

doxycycline, umbilical granuloma

Introduction

The umbilical cord is formed from the fusion of the yolk stalk containing the yolk duct and the body stalk containing the umbilical vascular and the allantois. It serves as a channel that allows blood flow between the placenta and fetus for material exchange. It also plays an important role in the development of the intestine and the urinary system. The yolk duct closes by 10 weeks of gestation. The allantois is obliterated at birth. At delivery, the umbilical cord is separated from the newborn, allowing an umbilical stump remaining. Shortly after birth, the umbilical vascular close. Normally, the remained umbilical stump separates by 4 weeks. After the umbilical stump falls off, the umbilical ring become epithelialized and is covered by skin and closed finally.[1]

Umbilical mass is common in pediatric surgery. Granuloma is the most common mass at the umbilicus in neonates and infants. Usually, it is presented with a pink to light reddish piece of tissue with drainage at the umbilicus. If not treated, the granuloma would persist after the separation of umbilical stump. The exact reason that some infants develop an umbilical granuloma while others do not has been underrecognized. Until now no evidence has suggested that there is any hygiene issue involved in its pathophysiology. Histologically, the lesion is granulation tissue composed of fibroblasts and capillaries. What causes the umbilical granuloma remains unknown, whereas it is indubitable that it is a product of inflammatory reaction with granulation tissue of overgrowth. No spontaneous resolution has been documented in the literature. Therefore, once the diagnosis is established, proper management is needed for this condition.

Tetracyclines are broad-spectrum antibiotics that act at the ribosomal level where they interfere with protein synthesis, indicated for use against many bacterial infections. Recent studies have suggested that tetracyclines not only have antimicrobial property but also anti-inflammatory and anti-angiogenesis effects. As anti-inflammatory and anti-angiogenesis agents, they are

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widely used in the treatment of various skin diseases.[2] For example, doxycycline is effective in the treatment of *acne*, particularly during the inflammatory stage. Currently, it is believed that the inflammatory reaction plays an important role in the pathophysiology of *acne*, and doxycycline can inhibit this reaction. For the treatment of *rosacea* with doxycycline, the actions that it can inhibit angiogenesis and inflammation may explain its beneficial effects.[2] Doxycycline and other tetracyclines are predicted to be similarly effective agents in other disorders in which the inflammatory reaction and granuloma formation are affected.

This case series represents a prospective evaluation of patients with umbilical granulomas. All patients were treated with topical doxycycline.

Patients and Methods

Criteria for enrollment were the following: (*a*) small, red, moist, and velvety mass at umbilicus with persistent discharge (for at least 2 weeks prior to enrollment); (*b*) absence of mucosa-like tissue remnant on the surface of lesion (for excluding umbilical polyp); and (*c*) absence of other pathologies (patent urachus, omphalomesenteric duct remnant, omphalocele, etc) by imaging examination.

The patients were randomly assigned into 2 groups: inpatient group and outpatient group. After informed consent had been obtained from parents or guardians according to institutional guidelines, the patients were treated with doxycycline. The protocol of doxycycline therapy was approved by the institutional ethics board at The Second Affiliated Hospital to Xi'an JiaoTong University.

Doxycycline powder was administered topically once daily. After clearing the discharge at the umbilicus, adequate amount of doxycycline powder (varying from 20 mg to 50 mg) was sprinkled finely over the whole surface of the lesion to make sure that the lesion was well covered by the agent, and the umbilicus was then well covered with dressing until the next administration. The lesion was reevaluated daily, and the treatment discontinued after 5 days as a protocol. The administration of the agent was performed by pediatricians in the inpatient group and by parents in the outpatient group. Cure was defined as complete regression and separation of umbilical granuloma. No response was defined as no regression of the granuloma, persistent umbilical discharge. The protocol was restarted when no response was observed. Lesions that showed still no response to 2 courses of treatment would been surgically resected.

The data were entered into a Microsoft Excel worksheet, and the Excel statistical formula function wizard was used to compare the sex ratio, age, and cure rate between 2 groups. Data were expressed as mean ± standard deviation. A value of $P < .05$ was considered significant. Additionally, the mean cost of therapy between the 2 groups was compared.

Table 1. Demographic Data of Patients Enrolled.

	Inpatient	Outpatient	*P* Value
No. of patients	24	60	
Sex ratio (male/female)	14/10	26/34	>.05
Age (days)[a]	81.08 ± 23.21	78.27 ± 31.89	>.05
Cure rate[b]	22/24	47/60	>.05
Cost[a]	226.52 ± 22.72	35.64 ± 10.86	<.05

[a]Data expressed as mean ± standard deviation.
[b]One course of treatment.

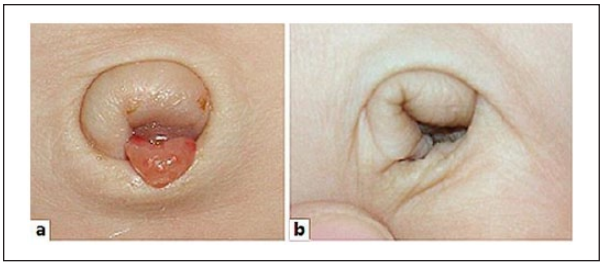

Figure 1. (a) Prior to treatment. (b) Posttreatment.

Results

Between June 2011 and July 2012, 84 patients, aged 28 days to 129 days (mean 65.3 days), were included in this study. There was not statistical difference in the sex ratio or the mean age between the 2 groups ($P > .05$; Table 1).

Inpatient Group

Twenty-four patients were assigned to the inpatient group. During the treatment, the umbilical granuloma gradually shrunk, darkened, turned black, and dried and separated within days (Figure 1). The discharge decreased and disappeared accordingly. Twenty-two patients of this group were cured by the aforementioned definition following one course of therapy. One patient was cured following 2 courses of therapy. One patient underwent surgical resection.

Outpatient Group

Sixty patients were assigned to the outpatient group. Forty-seven patients were cured following one course of

Table 2. The Characteristic of Current Therapies.

Current Therapies	Mechanism	Performer	Cost	Complications
Silver nitrate	Chemical burn	Professional	Low	Skin burn
Ligation	Avascular necrosis	Professional	Low	Lesion residuum
Electric cauterization	Electric burn	Professional	High	Operation associated
Surgery	Removal	Professional	High	Operation associated
Topical doxycycline	Anti-bacterium; anti-inflammation; hyperosmotic dehydration	Professional and parents	Low	Not observed

therapy. Thirteen patients showed no response to the treatment. They received the second course of therapy under our direction, and 9 patients were cured by the protocol finally. Four patients underwent resection of the lesion finally.

With one course of therapy, the statistical difference in response rate was not significant between the 2 groups (91.67% vs 78.33%, $\chi^2 = 1.27$, $P > .05$). The overall cure rate was 82.14% (69/84). With 2 courses of therapy, the overall cure rate was 94.05% (79/84).

Adverse Event

Among the patients enrolled, no discomfort of patient or change of surrounding normal skin was observed during treatment. Patients had been followed-up for 3 to 13 months, and no discoloration of surrounding skin or recurrence was observed.

Cost Comparison

The cost in the inpatient group was higher than that in the outpatient group (US$226.52 ± 22.72 vs US$35.64 ± 10.86).

Discussion

Granuloma is the most common mass at the umbilicus in neonates and infants. This disorder may cause infections such as omphalitis and necrotizing fasciitis, which can be life threatening. No spontaneous resolution has been documented in the literature.[3] Considering the potential adverse consequences, the lesion should be appropriately managed after the diagnosis is established.

Granuloma formation is associated with delayed separation of the cord and persistent inflammation. Consequently, application of topical antibiotics and elimination of the friction of a wet diaper may allow the granuloma to epithelialize.[4] In practice, however, topical antibiotics, such as mupirocin, rarely manage it successfully, which implies the inflammation that causes granuloma formation may be not due to pure bacterial infections. Thus, the antibiotic treatment is not the key point. Therefore, destructive treatments such as silver nitrate, ligation, electric cauterization, and surgery have developed, but there are some disadvantages with these managements (summarized in Table 2).

As a conventional management, a 75% silver nitrate stick was applied to dry the umbilical stump and cauterize the granuloma. The response rate is about 60%. Because of the presence of drainage, the granuloma should be cleared with gauze to avoid chemical burns or discoloration of the surrounding normal skin. Commonly it is administrated by professionals. More caution should be exercised to avoid leaking onto healthy tissue when repeatedly managing a large granuloma. Nevertheless, due to the movement of struggling infant, chemical burns have still been reported following leaking onto the surrounding tissue.[5,6] Ligation is another treatment. It is just applied to pedunculated lesions. There is no nerve within the granuloma, and ligating is painless.[7] To avoid lesion remaining, the most ideal level of ligation is the root of peduncle. In our experience, it is difficult to perform so accurately and expectantly because of infant struggling without general anesthesia. Sometimes a little part of the lesion remained with persistent drainage following ligation. An inevitable limitation of this technique is that it cannot be used to treat sessile lesions. Currently, electric cauterization or surgery is an option for those babies who failed previous noninvasive treatments.[1] These treatments are surgical removal of the granuloma under general anesthesia. A disadvantage is that it costs more than noninvasive treatments.

In our early practice, a baby with umbilical mass and drainage showed no response though 2 courses of doxycycline therapy given. Ultrasound examination was performed and an omphalomesenteric cyst was detected. She received surgical resection of the lesion later. Other pathologies such as patent urachus, omphalomesenteric duct remnant, and omphalocele were excluded in this study. In our study, topical doxycycline had a high response rate (94.05%) without recurrence. As mentioned above, doxycycline is not only an antibiotic but also an anti-inflammatory and anti-angiogenesis agent. These properties are speculated to be part of the therapeutic mechanisms involved in our study. Additionally, since

doxycycline of powdered formula was used topically and persistently, it seemed that the agent might act by hyperosmotic dehydration mechanism. However, this effect is not so powerful as to cause damage to normal surrounding keratinized skin when applied for short duration.

Among the tetracyclines, doxycycline has a lower avidity for calcium and lower potential for staining of teeth than others. Side effects of the doxycycline are associated with systematic administration for long duration. The risk of dental staining is considered negligible if treatment duration is less than a few weeks.[8] Nevertheless, in our treatment, the duration is less than a week, the agent is administered topically for external application, and the absorbance and bioavailability may be negligible. For these reasons, the risk of teeth staining may be largely reduced.

In our case series of the outpatient group, 10 patients were cured after the second course of therapy, in which the parents carelessly sprinkled the agent over only part of the lesion surface due to baby struggling and moving during the first course. The parents re-administrated the agent under our direction and these patients were cured after the second course of therapy.

Additionally, the outpatient group had the same response rate as inpatient group in our study. The agent can be conveniently performed by parents at home. Compared with inpatient treatment, the cost of outpatient treatment can be largely reduced.

Conclusion

The treatment of umbilical granuloma using topical doxycycline is safe and of high efficacy. The administration of the agent can be performed conveniently by parents at home, which can reduce the cost of therapy. This protocol could be considered to be the first treatment option for this disorder in neonates and infants. The therapeutic mechanisms involved in our study needs to be further studied and confirmed. The long-term effects on tooth development in children need to be further investigated due to the side effect profile of tetracycline-based antibiotics.

Author Contributions

HW contributed to conception and design; contributed to acquisition; drafted manuscript; critically revised manuscript. YG gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy. YD contributed to conception and design; contributed to analysis. BZ contributed to conception and design; contributed to analysis and interpretation of data. XG co-drafted the manuscript; critically revised the manuscript for important intellectual content.

Declaration of Conflicting Interests

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