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ORIGINAL ARTICLE

Medicated Manuka honey in conservative management of exomphalos major

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Abstract
Purpose The aim of this study was to assess the effectiveness of Manuka honey ointment and dressings in the conservative management of exomphalos major (EM).
Methods A retrospective review of five patients with EM who underwent non-operative management with Manuka honey ointments and dressings was carried out to assess the time to complete epithelialisation, time to full feeds, hospital stay, adverse effects, complications and outcome.
Results The skin epithelialisation over the EM sac was achieved in a median of 63 days (48–119). The median time to full enteral feed was 13 days (3–29). The median hospital stay was 66 days (21–121). No adverse effects were noted related to Manuka honey. Three patients had pulmonary hypoplasia requiring prolonged hospitalization; one of those died with respiratory complications at home after achieving complete epithelialisation. The follow-up was a median 16 months (6–22). Two patients did not require repair of the ventral hernia. One patient had ventral hernia repair at 16 months with excellent cosmesis. The remaining patient is awaiting repair.
Conclusion This is the first description of the use of medicated Manuka honey ointment and impregnated dressings in the conservative management of EM. This treatment is safe, efficacious and promotes wound healing with favorable outcome.

Keywords Exomphalos · Major · Omphalocoele · Management · Conservative · Honey dressing

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Introduction

Exomphalos major (EM) is an anterior abdominal wall defect containing abdominal viscera including liver, with an incidence of approximately 1.5–2.5 per 10,000 live births [1–3]. The primary surgical closure in EM is associated with significant morbidity due to the small peritoneal cavity. The major drawbacks include: kinking of inferior vena cava, bleeding from the liver, compartment syndrome, infection, wound dehiscence and respiratory compromise requiring ventilatory support. The traditional non-operative techniques in the management of exomphalos aim to sustain the sac, allowing granulation and skin epithelialisation over the ventral surface [4]. Infection leading to septicemia is the major risk of conservative management. The other complications include early sac rupture and evisceration.

Historic reagents namely, mercurochrome, iodine-based solutions and alcohol, were used to promote epithelialisation and aid sepsis control. Their popularity in the clinical practice has decreased due to concerns with systemic absorption and potential toxic side effects. Mercurochrome is associated with iatrogenic mercury poisoning, while reports by Cosman et al. raised concerns of hypothyroidism associated with topical administration of povidone iodine [5, 6]. Recent reports have described and recommended the use of silver-based products for the conservative management of EM [3, 4]. However, this practice has been questioned by Lewis et al. [7], reporting increased serum silver levels in two patients with EM treated at our center.

In the light of this concerning evidence, we looked for new products that can promote wound healing without adverse effects. Honey is a supersaturated sugar solution, derived from the nectar gathered and modified by bees (*Apis mellifera*) [8]. Honey has been used to treat acute and chronic wounds since ancient times. Historic documents, in

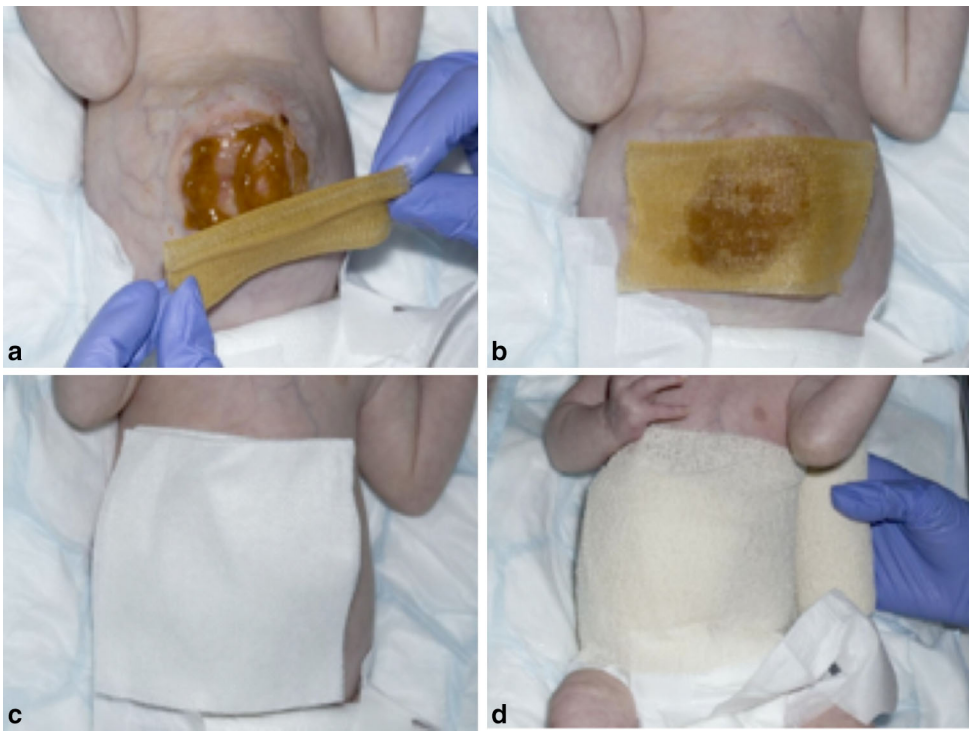

Fig. 1 Application of honey and dressing: **a** application of honey paste, **b** honey dressing, **c** sterile gauze placed on *top*, **d** completion of dressing with crepe bandage

various cultures, have described honey-based ointments used to treat burns and infected wounds [9, 10]. More recently, experimental data on animals showed that honey caused less oedema, fewer inflammatory cell infiltration, better wound contraction, improved epithelialisation and tissue strength [11]. Honey has a hyperosmolar effect, drawing fluid from the circulation and appears to provide a moist and nutrient rich environment, which improves tissue growth [8, 12].

Experimental studies have confirmed that honey stimulates the synthesis and improves the strength of collagen fibers [13]. Manuka honey is derived from *Leptospermum* tree species and is known for its antibacterial effect, independent of peroxide activity and osmolarity [12, 13]. The substance responsible for this has been termed Unique Manuka Factor, but its biochemical structure has not been yet identified [8].

We report five EM patients successfully managed conservatively using Actilite® (Advancis Medical), a non-adherent primary dressing impregnated with antibacterial Activon+ (Manuka Honey and Manuka Oil) and Activon Tube® medical grade Manuka honey.

Materials and methods

Between January 2009 and July 2012, five patients born with an antenatal diagnosis of EM underwent non-operative management. We obtained consent for the use of Manuka honey dressings and clinical photography from parents of all the neonates.

The exomphalos sac was cleaned initially with sterile saline. Manuka honey ointment (Activon Tube®) was then applied directly on the sac and dressed on top in a circumferential fashion with Actilite® honey-impregnated gauze. The dressings were kept in place with sterile gauze and a mildly compressive elastic crepe bandage (Fig. 1a–d). During subsequent dressing changes, the sac was irrigated with sterile saline before application of Manuka honey. No attempt was made to remove the residual honey, as this may traumatize the sac. Initially, the dressing was changed every 48 h to allow inspection of the sac. Following dressing changes, all patients were monitored for pain by the nurses using an analogue five-point pain chart. Once the process of epithelialisation started and the sac remained clear of infection with minimal exudate, we subsequently changed the dressings only twice weekly and towards the end of the treatment to once a week. The dressings were discontinued once full epithelialisation was achieved. Initially, the parents assisted and then were trained to do the dressings once the patient was discharged to home.

The patients' nutritional status was monitored clinically with weight and head circumference checks and input from a dietitian for their increased calorie requirements. Throughout the inpatient stay the infants were monitored for signs of sepsis and wound healing. The inflammatory markers (C-reactive protein and white cell count) were monitored every 2 weeks or more often if sepsis was

suspected. Blood glucose was monitored once per week. Weekly culture swabs from the exomphalos sac were monitored during the initial phase of treatment.

The criteria for discharge from the hospital were: infants tolerating full enteral feeds and maintaining expected growth, no signs of sepsis, reasonable epithelialisation of the sac, parents trained to change the dressings and no major co-morbidity requiring inpatient support.

Results

The patients' demographic details, associated co-morbidities and outcomes are summarized in Table 1. There were no associated chromosomal abnormalities in any of the patients. The initial wound dressing in our first two cases in the series was Urgotul® (Urgo Medical), Urgotul Silver® (Urgo Medical) and silver sulfadiazine ointment. We introduced medicated Manuka honey dressings during these two infants inpatient stay as their initial conservative management was complicated by episodes of local and systemic infections and the parents were distressed by the strong, offensive odor emanating from the slough covering the sac. They were converted to Manuka honey dressings in accordance with our experience with our third patient. Following the change to Manuka honey dressings these two infants did not develop any further infections, the odor disappeared and they were discharged home. The other three patients were managed from birth exclusively with Manuka honey ointments and dressings.

One extremely premature infant (gestational age 28 weeks and a birth weight of 910 g) with significant respiratory distress and other prematurity related co-morbidities was managed conservatively with Manuka honey ointments and dressings at the local neonatal unit under the surveillance of our outreach team (surgeon, specialist nurse). She had a relatively small abdominal cavity and she was considered not safe for transfer to our unit.

The patients reached full enteral feeding requirements (oral or nasogastric tube) at a median of 13 days (range 3–29). Full epithelialisation and discontinuation of treatment was achieved in a median of 63 days (range 48–119). Total hospitalization time was a median of 66 days (range 21–121). One infant with significant pulmonary hypoplasia required a prolonged admission despite complete epithelialisation

Table 1 Patients' demographic details

Gender	Gestational age	Birth weight (g)	Co-morbidities	Size of defect and contents of the sac	Length of treatment (days)	Length of hospitalization (days)	Outcome
F	38 + 5	2,650	Patent ductus arteriosus Patent foramen ovale	6 cm, liver in the sac	63	21	Well, awaiting ventral hernia repair
M	34 + 5	2,025	Patent ductus arteriosus Atrial septal defect Pulmonary hypoplasia Persistent pulmonary Hypertension Undescended testis Hemivertebra T7	15 cm, liver in the sac	119	121	Died at home due to respiratory compromise
M	39 + 2	3,490	No	9 cm, liver in the sac	58	21	Well. Right inguinal hernia repaired at 16 weeks. Ventral hernia repaired at 16 months
M	37 + 0	3,060	Laryngomalacia Tracheal stenosis Tracheostomy Pulmonary hypoplasia Hypospadias Gastro-oesophageal reflux Patent ductus arteriosus Left inguinal hernia	8 cm, liver in the sac	99	88	Well, minimal abdominal wall defect
F	28 + 1	910	Pulmonary hypoplasia Left inguinal hernia	5 cm, liver not in sac	48	66	Well. No ventral defect. Left inguinal hernia repaired

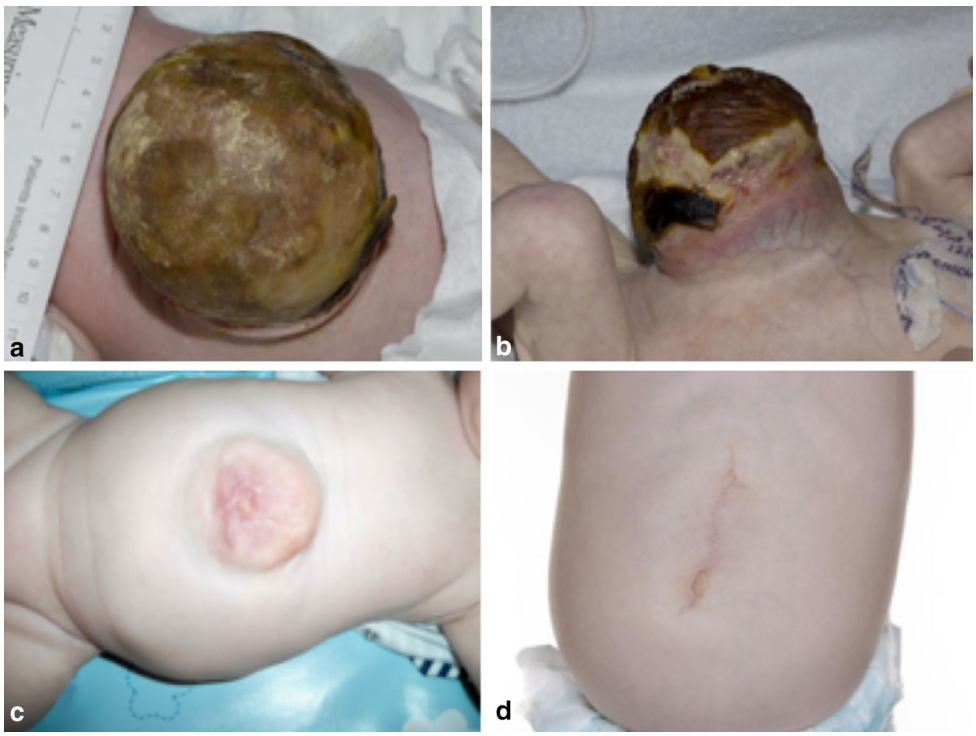

Fig. 2 Various stages of the healing process (Case 3, Table 1) EM with 9 cm abdominal wall defect (**a**). Conservative management was started on day 1 of life, using Activon Tube® ointment and Actilite® Manuka honey dressing. Initially, the dressing was changed on alternate days for 11 days then twice a week. On day 21 of life the patient was discharged home. The epithelialisation process had advanced half way up the sides of the defect by day 39 (**b**), and by day 59, full epithelialisation was achieved (**c**). This patient had delayed closure of his ventral hernia at 16 months with excellent cosmetic result (**d**)

because of ongoing social issues and the need to organize home oxygen support. A second patient had a prolonged hospitalization due to severe laryngomalacia requiring a tracheostomy.

In one case, *Klebsiella* grew from the surveillance swabs taken from the sac and required a course of prophylactic antibiotics (Co-Amoxiclav) for 7 days following advice from our microbiology department to prevent systemic spread. There were no signs of systemic sepsis or raised inflammatory markers. Another patient with clinically suspected sepsis was managed with broad spectrum oral antibiotics (Co-Amoxiclav) for 5 days. In both these cases the blood cultures remained negative. No side effects from using Manuka honey dressings were noted (hyperglycemia or adverse skin reactions).

Dressing changes were tolerated well by all patients and none of them had recorded an increased pain score. These infants did not require any analgesia during or following the dressing changes.

All patients were followed up after discharge for a median of 16 months (range 6–22). One patient with preexisting pulmonary hypoplasia died 3 months after discharge with respiratory complications. Two patients had a very good cosmetic outcome and did not warrant a ventral hernia repair. In one case the ventral hernia was repaired at 16 months (Fig. 2a–d). The remaining patient is clinically very well and she is awaiting repair of the persistent ventral defect.

Discussion

The management of EM remains a significant surgical challenge. Over the years, multiple methods and dressings have been used, with various degrees of success. This is the first description of the use of medicated Manuka honey in the management of the exomphalos sac, achieving successful epithelialisation of the skin with minimal morbidity. Additionally, the Manuka honey dressing changes were well tolerated by all five EM infants and were not associated with malodour. In two of our cases, the ventral defect did not require operative closure. The scar contracture not requiring a formal repair of the residual ventral hernia was also seen in cases where silver-based products were used [3].

Our experience with Manuka honey dressings showed encouraging results and prevented septic episodes in these infants. A Cochrane review in 2013 reported on 25 adult trials with honey dressings and concluded that honey might be superior to some conventional dressing materials, but raised concerns about the replicability and applicability of this evidence [8]. No significant adverse events following medical use of honey have been reported in this review and in our study. In a randomized clinical trial of honey-impregnated dressings, pain was reported as the most common side effect in treatment of leg ulcers in adults [14]. Pain is thought to be related to the acidity of the honey [15]. In our series both parents and nursing staff reported that these infants tolerated dressing change well

without any need for analgesia. The sac remained intact in all cases, with no ulceration or bleeding observed.

With conservative management, infection and septic episodes are major sources of morbidity. Our five EM infants were closely monitored for sepsis with culture swabs and inflammatory parameters. We believe antibacterial properties of Manuka honey may have been responsible for preventing septic episodes in our cases. Sepsis-related mortality in EM can be associated with central venous lines or sub-eschar infection [3, 16]. Most recently published series successfully managing EM recommended silver sulfadiazine dressings probably due to non-availability of alternatives and for its antimicrobial properties [3, 7, 17, 18]. However, increased blood levels of silver >200 times in conservatively managed EM cases have been reported with topical application of silver products, raising concerns of possible associated long-term silver toxicity [7]. Although not routinely monitored, it is worth noting that silver toxicity is not reported in conservatively managed cases of EM in many of the series recommending the use of silver dressings [3, 4, 18].

One patient in our series died due to associated pulmonary hypoplasia and respiratory complications at home after successfully achieving complete re-epithelialisation. Pulmonary hypoplasia and pulmonary hypertension are described in 50 % of EM cases and respiratory complications with related mortality have been reported in other series [3, 16, 19]. A large study assessing pulmonary function in EM found lung volume restriction without airway obstruction and reduced respiratory compliance [20]. In our series, apart from this infant, two other infants with EM also had a mild degree of pulmonary hypoplasia.

Botulism in infants has long been associated with the ingestion of honey [21, 22]. The risk of botulism is eliminated through gamma irradiation of the dressings, which is now a standard practice. The process of irradiation does not reduce the antibacterial effect of the honey [22]. There is no evidence in the literature to suggest systemic side effects of honey. Hyperglycaemia and systemic absorption after honey dressings have not been reported in the literature and honey has been successfully used in treatment of ulcers in diabetic patients [23, 24]. In our exomphalos infants managed with honey, blood sugars were routinely monitored and no hyperglycaemic episodes were recorded. The incidence of honey allergy has been reported to be 2.3 % in a study of 173 patients with food allergies [25]. There is no convincing evidence regarding allergic reactions to topical honey, but the manufacturers are advising caution in the use of honey-based products if there is known allergy to bee stings or bee products. No allergic reactions have occurred in our patients.

In summary, the use of Manuka honey topical agents and impregnated dressings in the conservative management of exomphalos is safe, efficacious and easily accepted by the parents. Further studies are warranted to define its efficacy, side effects, infection episodes and cost effectiveness in a pediatric setting.

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