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ORIGINAL ARTICLE

Pleurodesis for effusions in pediatric oncology patients at end of life

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Abstract
Background Pleurodesis for end-of-life care has been used in adults for decades, but little is known about the usefulness of this technique in improving the quality of care for pediatric patients.
Objective To assess whether intractable pleural effusions in pediatric oncology patients at end of life could be sufficiently relieved by pleurodesis.
Material and methods Eleven pleurodeses were performed with doxycycline in seven pediatric cancer patients (age 3–21 years) with intractable pleural effusions at the end of life. Five patients had unilateral pleurodeses and two had a unilateral followed by bilateral pleurodeses.
Results Respiratory rates decreased in all seven patients (P=0.016) and aeration improved significantly after chest tube placement (P=0.033). The chest tubes were placed a median of 1 day before pleurodesis. Eight of nine chest tubes (89%) were removed before discharge at a median of 3 days after pleurodesis. Pain secondary to the pleurodesis lasted 1 day or less. Improvement in the respiratory rate remained after pleurodesis and chest tube removal (P=0.031). Five of seven patients (70%) were able to leave the hospital to return home. The five patients discharged lived 10 to 49 days (median 19 days) after discharge.
Conclusion Pediatric oncology patients with intractable effusions at end of life can have respiratory benefit from pleurodeses and, as a result, are more likely to return home for terminal care.

Keywords Palliative care · Pleurodesis · Interventional procedures · Children · Lung neoplasms

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Introduction

No pediatric oncology series has been published describing the palliative benefit of pleurodesis in end-of-life care, although the technique has been used in adults for decades [1]. The purpose of this study was to evaluate the quality of life following the improvement in respiratory status in pediatric patients with malignant pleural effusion treated by thoracostomy and pleurodesis at end of life.

Materials and methods

We retrospectively reviewed the medical charts (N.O.), imaging records (F.A.H.) and procedure records (N.O. and

F.A.H.) of patients at one pediatric cancer institution in whom pleurodesis was performed between August 2001 and December 2005. The local human research protection board approved this review. The Health Insurance Portability Assurance Act compliance was not breached, as all patients died before this review was undertaken.

There were seven patients in the study, five males and two females; two had pleurodeses of both lungs comprising a total of nine studied lungs. The median age was 15 years (range 3–21 years). Seven distinct tumors were represented in the patients, including Hodgkin disease, hepatocellular carcinoma, Ewing sarcoma family of tumors, rhabdomyosarcoma, osteosarcoma, malignant peripheral nerve sheath tumor and neuroblastoma. Patients had chest tubes placed when they were symptomatic with tachypnea or shortness of breath or if they were found to be hypoxic in room air. Patients and parents were told of the option of pleurodesis when consenting for chest tube placement.

The nine chest tubes were placed 0–19 days (median 1 day) before pleurodesis under general anesthesia. Typically 10F pigtail drainage catheters [2] were placed by sonographic (Fig. 1) and fluoroscopic guidance with a Seldinger technique. A sample of the pleural fluid was sent for cytology. In one instance an 8F catheter was placed (Fig. 2) and then replaced with a 10F catheter at the time of the pleurodesis. All other patients who received a chest tube had a pleurodesis through it before the chest tube was removed.

The pleurodesis was performed by first aspirating all the pleural fluid possible with a syringe. Then 500 mg doxycycline was mixed with 40 ml normal saline [3]. Two patients (one as young as 3 years) had repeat pleurodeses with 500 mg doxycycline in each pleural space. The pleurodesis itself was performed with intravenous narcotics at the bedside in the first patient. Only the first three sclerosant injections in one patient contained 20 ml 1% lidocaine. Upon completing the first instillation, this mixture was so painful (10 on a scale of 0–10) that the sclerosant was removed, with an immediate reduction in the pain. The pain team then prescribed patient-controlled analgesia. That first patient was asymptomatic the next day. All future pleurodeses were performed under general anesthesia. The mixture was injected into the pleural cavity through the chest tube and the tube was clamped for 20–30 minutes. The patient was moved into various positions: supine, decubitus, and nearly prone, tilting the head down and up. Then the fluid was removed with a syringe and the chest tube was again attached to a wet drainage system with 20 ml H_2O of wall suction. Patient-controlled analgesia was prescribed by the pain team and initiated on recovery. All patients except one remained in the hospital until the chest tube was removed. The chest tube was removed when the pleural drainage became less than 10 ml/h.

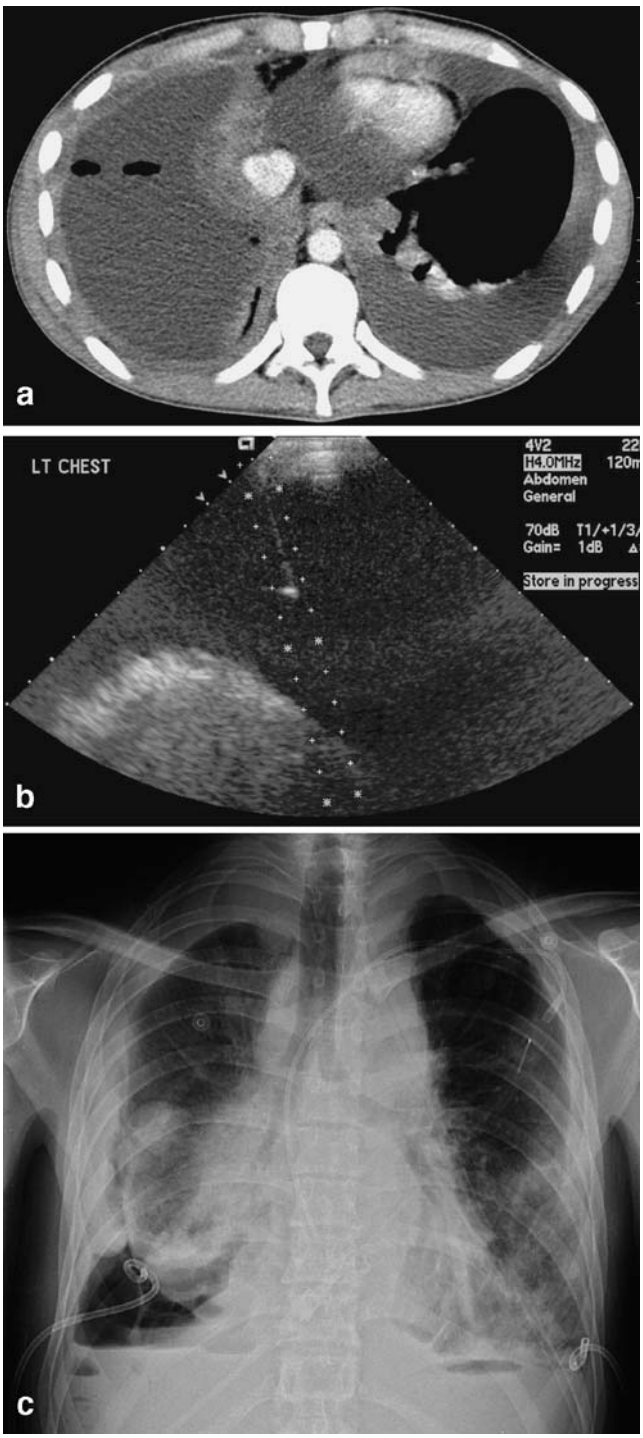

Fig. 1 A 21-year-old man with metastatic rhabdomyosarcoma. **a** CT shows bilateral pleural effusions with loculated air in the pleural cavity on the right. **b** Sonographic guidance of the pleuracentesis. The left pleural fluid is echolucent and was not malignant. A chest tube was placed and left pleurodesis performed. **c** Chest radiograph after bilateral chest tube placement and bilateral pleurodeses shows a right loculated pneumothorax caused by a bronchopleural fistula obtained during vigorous suctioning at the end of the pleurodesis. The fistula closed the next day. The right effusion was malignant, draining 490 ml in the first 24 h after pleurodesis. The right chest tube remained until his death at home 21 days later. After the second left pleurodesis the left catheter drained 90 ml in the first 24 h and was removed on the 4th day at discharge

Data collected included gender, age at diagnosis and pleurodesis, diagnosis and patient pain self-assessment. Three indicators of lung well-being were measured: respiratory rate (RR), percentage O_2 saturation (pulse oximetry), and O_2 support (liters per minute, typically by nasal cannulae). The percentage aeration of each lung was estimated by one radiologist (F.A.H.) visually comparing the size of the aerated lung with the size of the hemithorax on the available chest radiographs and chest CT scans. Measurements of these five indicators were taken at four time points: prior to chest tube insertion, immediately after chest tube insertion, after removal of the chest tube, and at the time of the final clinical encounter in the study setting. In addition, drainage (milliliters) from the chest tube was measured at four time points: 24 h after insertion of chest tube, 24 h prior to the pleurodesis, 24 h after the pleurodesis, and 24 h prior to chest tube removal. The amount of pleural effusion or pleural peel was estimated as a percentage of the thoracic volume on the last available chest radiographs or CT scans.

The data were longitudinal in nature. Drainage was compared between time points in a pair-wise fashion by using the exact Wilcoxon signed ranks test that takes pairing and small sample sizes into account [4]. Drained and undrained lungs were considered independent out of necessity and were compared using the exact Wilcoxon test [5]. P values <0.05 are referred to as significant, but the results should be interpreted bearing in mind the retrospective and exploratory nature of this study. Patients were dichotomized according to whether the amount of fluid drained in the 24 hours prior to the procedure was above or below the median drainage for all patients. The lung with the greater drainage was used to assign each patient. Survival after pleurodesis was evaluated by the method of Kaplan and Meier and was analyzed with the exact log-rank test [6]. All patients were followed until death.

Results

Respiratory rate decreased in all seven patients after chest tube placement ($P=0.016$). Respiratory rate remained low after pleurodesis at the time of chest tube removal ($P=0.031$). However, by the last clinical encounter, the RR had risen to 28 breaths per minute (bpm) to nearly the predrainage rate (30 bpm). Supplemental oxygen was necessary in five patients

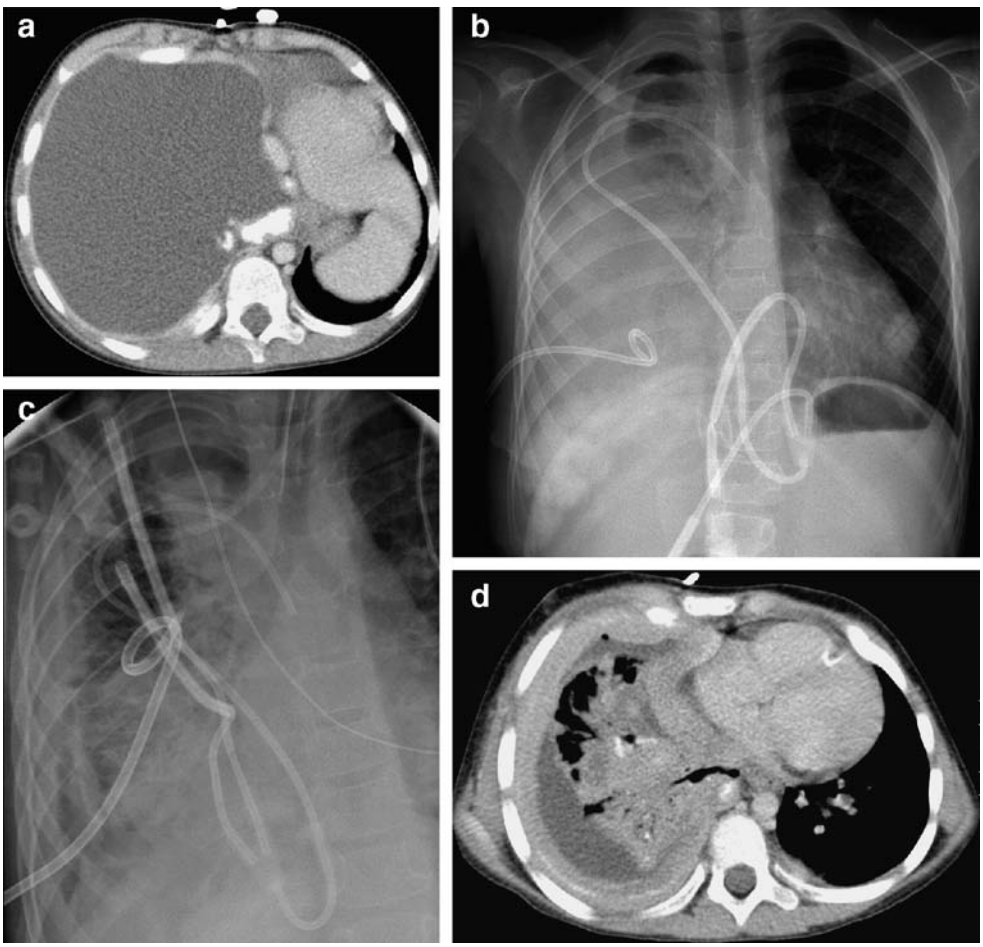

Fig. 2 A 7-year-old girl with multifocal and metastatic osteosarcoma. **a** CT scan demonstrates a large right pleural effusion and ossified metastases to the right rib, pleura and lung. **b** An 8F catheter was placed but not aspirated. It was simply placed to waterseal with wall suction. The radiograph shows that the right pleural effusion was not fully drained. This fluid was cytologically negative for tumor. **c** The catheter was exchanged 10 days later for a 10F catheter and placed superiorly. The doxycycline injection was performed there for 20 min and then the material was withdrawn. The catheter was then pulled back inferiorly and the doxycycline reinjected for an additional 10 min. **d** CT performed 9 days later shows a right pleural peel, pleural effusion, lung infiltrates and tumor with only 25% of the right lung aerated. At autopsy 49 days after the right pleurodesis, the right chest was full of tumor and the left chest contained 600 ml of pleural fluid

before the procedure and in five patients after chest tube placement, with one patient coming off supplemental oxygen and one patient requiring it after chest tube placement.

The aeration of the lungs that were treated improved from before to after chest tube placement (P=0.039) but the aeration decreased from after chest tube placement to the last encounter (P=0.031). Autopsy in one patient (Fig. 2) revealed a massive tumor on the side of the prior pleurodesis without pleural fluid.

For the lungs on the side where the pleura was not treated with drainage and pleurodesis, no two time points had significantly different aeration; all P values were >0.500. However, when comparing the treated and the untreated sides, initially the untreated side was worse (P= 0.007), but at the last encounter the aeration of the treated and untreated sides was not significantly different. Autopsy in one patient (Fig. 2) revealed 600 ml of pleural fluid on the untreated side.

Drainage in the immediate 24 h prior to pleurodesis ranged from 40 ml to 1,580 ml (median 200 ml), including 500 ml in one patient who was discharged from the hospital the next day with a chest tube. Only three of the pleural drainages revealed malignant tumor on cytology. Tubes were maintained (n=9) from 2 to 47 days with a median duration of 5 days. Eight of nine chest tubes were removed 1–28 days (median 3 days) after pleurodesis. Drainage continued to decline across the four times at which it was measured. Nine hemithoraces treated had a residual pleural peel or effusion of 10–40% of the thoracic volume (median 30%). Five of the untreated hemithoraces had 0–50% effusion or pleural peel (median 30%).

We were interested in determining whether the rate of pleural fluid production prior to pleurodesis was related to patient survival. Survival was compared between patients who had above and those who had below the median drainage in the 24 h before pleurodesis. The two curves showed the potential for those with more drainage to have a worse outcome, or fewer days of survival, but this cannot be verified nor refuted, necessarily, given the small numbers (P=0.114).

Two patients continued to have fluid production after the first pleurodesis and had the pleurodesis repeated on the ipsilateral side and performed on the contralateral side. They may be judged as initial failures in terms of fluid production, but they still showed an improvement in RR. The first patient had an unresected primary intrathoracic neuroblastoma, negative pleural cytology but probable lymphatic obstruction from a mediastinal lymph node metastasis. He had ipsilateral drainage of 200 ml in the 24 h before his first pleurodesis and 390 ml in the 24 h 7 days after his first pleurodesis. His second pleurodesis at that time allowed removal of the chest tube 21 days later, with only 10 ml of drainage in that tube prior to removal. He had that same chest tube in for 47 days, but both chest tubes were removed before his death in the hospital.

The second patient to have repeat pleurodeses had rhabdomyosarcoma metastases and was anxious to get home. After chest tube placement drained 1,500 ml of fluid that was negative on cytology, he had the left pleurodesis performed under the same anesthesia. Because 700 ml of drainage occurred during the subsequent 24 h, suggesting that the pleurodesis had failed, a repeat pleurodesis in the same pleural space was completed. During that second procedure, he had a right chest tube placement that revealed malignant pleural fluid, prompting a right pleurodesis. Unfortunately, during the removal of the doxycycline from the right chest, the syringe suctioning of the chest tube caused a bronchopleural fistula and a small pneumothorax (Fig. 1). The air leak resolved within 24 h. Because this patient was anxious to be discharged home that day, the left chest tube was removed before discharge but the right chest tube remained for 21 days until his death at home.

No other patient had any complications. Among the seven patients, pain from the pleurodesis ranged from 4 to 10 (median 5) on a scale of 0 to 10 for a duration of 1 day or less. Five of seven patients were on supplemental oxygen at the last clinical encounter before their death. The median duration of hospitalization following pleurodesis was 4 days, with hospitalizations ranging from 1 day to 34 days. Five of seven patients were able to leave the hospital to return home. The five patients discharged lived 10 to 49 days (median 19 days) after discharge.

Discussion

The success of the pleurodeses in these pediatric oncology patients cannot be measured simply in terms of the results documented above. To be able to return home without a chest tube and be relatively comfortable at home for a period of time before death is invaluable for most patients and their family. The one patient who left the hospital with a chest tube did so because of a pressing need to return home. Only two families opted for terminal care in the hospital and with the explanation that they felt more secure in the hospital with the changing conditions and needs of their dying child.

The available literature involving adult patients and the views of interventional and surgical clinicians indicate that a pleurodesis cannot be successful if there is a high rate of pleural fluid production. Because of this, we initially waited until pleural fluid production had decreased before attempting pleurodesis. However, we learned that the pleurodesis could be performed on the same day as chest tube placement; the benefit of doing both procedures on the same day was being able to

avoid a second anesthesia and decreasing the hospital stay. The median time between drainage and pleurodesis in our experience was 1 day. We only repeated the pleurodesis in two patients (Fig. 1).

We also examined the relationship between the rate of pleural drainage immediately preceding the pleurodesis with the patient's length of survival. There was a shorter survival in patients who had more than the median 200 ml drainage in the 24 h preceding pleurodesis; all three had died by day 21. Those four who had a lower amount of drainage prior to pleurodesis had all died by day 50 after pleurodesis. This link between rapid pleural fluid production and poor prognosis more likely reflects the virulence of the tumor rather than the effect of treatment. This was also demonstrated by the poor respiratory status of the patient at the last clinical encounter and poor aeration of the ipsilateral lung at the last imaging encounter. This was confirmed by autopsy to represent only tumor in the one patient examined (Fig. 2).

This brings up one concern. Does pleurodesis encourage angiogenesis and tumor growth? It has been demonstrated that vascular endothelial growth factor and angiogenesis play a pivotal role in pleurodesis [7] when using either transforming growth factor beta2 or doxycycline [8]. The opposite might also be true. The use of fibrinolytics might also cause angiogenesis by breaking down the fibrotic barrier between the blood supply of the tumor and that of normal tissue [9].

Pleurodesis is performed by some pediatric surgeons, most recently through video-assisted thoracic surgery. Physical pleurodesis is performed by gauze abrasion or electrocoagulation of the parietal pleura followed by chest tube drainage [10]. Because of the painful nature of this procedure, these children are also anesthetized and given narcotics following the procedure.

Outcome data available from metaanalysis in 2,053 mostly adult patients with malignant effusions suggest that thoracoscopic talc insufflation is the most effective method of pleurodesis, with the least recurrent effusions compared to bleomycin, tetracycline, doxycycline and bedside talc slurry administration [11]. The strategies of rolling the patient after instillation of the sclerosing agent or using protracted drainage of the effusion or larger chest tubes do not have substantial advantages [11].

Placing long-term tunneled pleural catheters is an alternative to the above methods and is associated with spontaneous pleurodesis in 42% of patients (15 of 31); continued drainage without pleurodesis controlled the effusions in 48% (15 of 31) [12]. In another series, catheters were maintained for a median duration of 56 days [13]. Intermittent drainage through the catheter was performed by the adult outpatient.

In conclusion, pediatric oncology patients with intractable effusions at end of life can derive respiratory benefit from pleural drainage and pleurodeses and, as a result, are more likely to return home for terminal care. Success of pleurodesis does not depend on the amount of previous pleural fluid production.

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