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RESEARCH ARTICLE

INTRAPLEURAL IRRIGATION WITH ELECTROLYZED SALINE FOR ACUTE EMPYEMA

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ABSTRACT

Background: The bactericidal activity of electrolyzed saline (ES), a novel disinfectant, was preliminary reported in the acute empyema. The efficacy of intrapleural ES irrigation against empyema was evaluated.

Methods: A retrospective study of fifty-four patients with parapneumonic empyema from 2005to 2016. Twenty-eight patients had ES irrigation under miniaturized thoracoscopic surgery or indwelled catheter (ES group). The remaining 26 patients had catheter drainage with or without saline irrigation (Control group). End points were disease cure, hospital discharge or prognosis at 5 months across subgroups defined by patients characteristics, disease severity, and treatment procedures.

Results: Most pathogens were oral microflora. None in the ES group had subsequent surgical options, whereas five in the control group were followed by surgical options. Clinical features were promptly improved in the ES group. Mean catheter indwelling periods in the ES and control groups were12.3±10.0 and23.9±19.7days (p=0.0080), respectively. Disease cure rates were 89.3% with 9-dayand 50.0% with 34-day half-cure periods, respectively, with significant improvements in the ES group (p<0.001). The midpoint of hospital stay and mortality in both groups were37 and 77days (p= 0.0496), and 14.3 and 42.3% (p= 0.0216), respectively. The disease free survival rates at5months were 75.4% and 45.0% (p=0.0066), respectively. Intrapleural ES irrigation was a significant contributor for outcome improvements of parapneumonic empyema, while age, comorbidities, bronchofistula, and disease extensions were other prognostic limitations under multivariable analysis.

Conclusions: ES irrigation was an effective and minimally invasive strategy for rapid cure of empyema.

INTRODUCTION

The key treatment of empyema is cleansing and closure of the empyema space for the relief of septic conditions, facilitation of pleural epithelialization, and diminishing bacterial colonization[1-4]. The current strategy for achieving this frequently requires an invasive surgical approach with a long-term hospital stay[2-5]. We have reported the preliminary bactericidal activity of electrolyzed saline (ES), a novel disinfectant, with prompt cure of acute empyema[6]. This paper describes a study on the efficacy of intrapleural ES irrigation compared with conventional conservative treatments for acute bacterial empyema.

METHODS

Study Oversigh

The Institutional Review Board of our hospital granted ethics approval for this study (IRB #2602, SMH, March 24, 2015). Individual patient consent was obtained.

Patients

We had 76 consecutive patients with acute empyema between October 2005 and December 2016. Twenty-two patients with traumatic or postoperative empyema of lung or esophageal resections, tuberculous empyema, parapneumonic empyema primarily chosen for surgical options or parapneumonic effusions with negative bacterial cultures were excluded. Twenty-eight of the remaining 54 patients managed with ES irrigation (ES group) and the remaining 26 with conventional conservative management (Control group) were enrolled in this retrospective study. Patient prognosis was evaluated by patient characteristics, age, Charlson comorbidity score [7](CCS), disease characteristics of severity, empyema extension, bronchopleural fistula, residual pleural space, and treatment procedures. A CCS of zero indicates no comorbid conditions, whereas a score of 3 or greater indicates the greatest extent of comorbidity. The empyema extension from the apex to the diaphragm was defined as total empyema, and

other localizations were defined as localized empyema. Treatment procedures were irrigations with ES or physiological saline under mini-thoracoscopy[8] (mini VATS), mini VATS with indwelled catheter or indwell catheter alone, or non-irrigations with catheter drainage alone.

Follow-up

Patients were followed-up for five months, during which all disease-related events occurred in this study after the treatment commencement. Patients discharged from our institute were followed-up at our outpatient clinic or by phone interview with their primary doctors. Patients were followed up by clinical features of febrile time, parenteral antibiotic periods, indwell catheter periods or interval of miniVATS, CRP of inflammatory markers 1 week after treatment commencement, and adverse effects of irrigating chest pain. Empyema space was followed up with a plain chest X-ray, CT scan, ultra-sonogram or thoracentesis. The first endpoint was disease cure, second was hospital discharge, and third was mid-term prognosis at5months.

Treatment definitions

Treatment period was defined as that between initial miniVATS or catheter indwell and final mini VATS or indwell catheter removal. The treatment period of single mini VATS counted for one day. The date of disease cure defined as that of catheter removal, final mini VATS with negative bacterial cultures of pleural effusions, cleared effusions or closure of the pleural space. Treatment failure was defined as patient death, treatment suspension, disease relapse, or conversion to surgical options such as open thoracostomy, thoracotomic decortication, or closure of the bronchofistula. Others were defined as successful treatment.

Custom Made ESPreparation

ES aqueous solution was produced from 0.1% salt tap water mixture using a water electrolysis generator (Oxilyzer Medical C-L, Koken Ltd., Tokyo). Electrolyzed strongly acidic water with a pH of less than 2.7 was generated at the anode compartment and was collected for use in irrigation. ES solution itself is a sterilizer of routinely washed and dried medical instruments, and sterilization was unnecessary in ES preparation.

Criteria for Procedures

Mini VATS debridement was applied for removal of mass fibrin debris, or multiple fibrin septations detected on CT or ultrasonography. Mini VATS was not applied to patients who had sufficient catheter drainage or to patients whose performance status did not allow for mini VATS procedure. In the era before routine use of ES, catheter drainage alone or combined continuous saline irrigation was the routine procedure for acute empyema in the Control group.

Mini VATS and Catheter Indwelling Procedure

The detailed procedure of mini VATS under locoregional anesthesia with or without paravertebral intercostal nerve block was as previously described [8]. A utility thoraco-port for the removal of fibrin debris, purulent effusions, ES topical irrigation, and monitoring using a minithoracoscope (2.9 mm Ideal Eyes, Stryker Co., MI) was produced at an appropriate site as detected on the ultrasonogram. If the scope monitoring disturbed the handling of other operating tools, an additional site was created using a needle port (2/3mm Endopath Bladeless Trocar, Johnson & Johnson, NJ) for the mini thoracoscope. Fibrin debris was removed as much as possible in the dead space to forma single lumen, and the pleural cavity was washed out and cleaned by topical irrigation with two or three liters of warmed ES solution. At the end of the procedure, a double-lumen silicon catheter (Fr18 Phicon Samp Catheter, Fuji Systems Co., Tokyo) for continuous ES irrigation and pleural drainage at low-pressure suction was indwelled into the dead space cavity until the clinical features improved, and the drained fluid became clear and demonstrated negative bacterial cultures. Manual catheter indwelling was performed under fluorescence for other patients of non-indicated mini VATS.ES solution was continuously dripped at a rate of 80~150ml/hr through the inflow of the double-lumen catheter.

Statistical Analysis

For comparisons of patient characteristics and outcomes between two groups, χ^2 tests were used for categorical variables, and Student's *t*-tests were used for continuous variables. The data of continuous variables were expressed as mean ± standard deviation. The cumulative disease rate, hospitalization rate, and mid-term survival rate were estimated using the Kaplan-Meier methods, and a Cox proportional hazards model was used for the contributions of prognostic factors. A p-value less than 0.05 was defined as significant. Microsoft Excel software (Excel statics 2015; Ekuseru-Toukei 2015, Social Survey Research Information Co. Ltd, Tokyo) was used in statistical analysis.

RESULTS

Patient characteristics and pathogens

The follow-up times for ES and Control groups were 476±581.3 days and 288.3±506.5 days (p= 0.2116), respectively. No patients were lost to follow-up within 5months after the treatment commencement except two patients, one in each group, who were lost to follow-up at day 97 and 103, respectively. The number of patients in the ES group significantly increased soon after ES irrigation became the first choice for acute empyema based on our preliminary study[6]. The ES group included younger and better performance status patients who may have been primarily candidates for surgical options in the era before routine use of ES irrigation. Most patients of both groups had mild or severe comorbidities with elevation of CCS, such as chronic pulmonary insufficiency, an immunosuppressive status with severe diabetes mellitus, steroid-dependent connective tissue disease, mental disturbance of senile dementia, depression, mental weakness and schizophrenia, chronic heart failure, post cerebral vascular attack with dysphagia, or intrapleural malignancies. The gender and affected side ratio were almost the same in both groups. The etiology of the empyema were bacterial or fungal pneumonia, ruptured lung abscess, chronic infection with bronchiectasis, or unknown causes. One in the ES group had empyema of the post-pneumonectomy space in which aspiration pneumonia of the contralateral lung progressed. Disease severity was almost the same in both groups, including bronchofistula (Table 1). Frequently detected pathogens were bacilli and fungi, including Methicillin-resistant *Staphylococcus aureus* (MRSA).Most of the pathogens were oral microflora (Table 2).

Table 1 Patient characteristics

Patient characteristics	ES group	Control group	p-value
Follow-up time (days)	476.6 ± 581.3	288.3 ± 506.5	P=0.2116
Number of patients (lost)	28 (1)	26 (1)	
2005-2010/2010-2015	3/25	16/10	p <0.001
Age (years old)	65.2 ± 14.8 (27 90)	76.3 ± 13.6 (30 94)	p=0.0023
Gender. male/female	23/5	20/6	p= 0.6340
Charlson Comorbidity Score: 0/1~2/2<	7/ 12/ 9	1/ 10/ 15	p=0.0470
Affected side: right/left	13/ 15	12/ 14	p=0 .9839
Empyema extent: total/localized	11/ 17	13/ 13	p=0 .4285
Bronchopleural fistula: no/yes	25/3	20/ 6	p=0 .2232
Cause: pneumonia/chronic infection/unknown	19/4/5	16/ 3/7	p=0 .7189

ES: electrolyzed saline

Table 2 Pathogens of empyema

Pathogen*	ES group	Control group
Streptococcus strain	8	14
Staphylococcus strain	2	5
(MRSA	2	2)
Peptostreptococcus strain	4	3
Fusobacterium strain	6	1
Klebsiella pneumoniae	3	2
Pseudomonas aeruginosa	2	1
Escherichia coli	1	1
Parvimonas strain	1	
Haemophilus influenzae	1	-
Actinomyces meyeri	1	-
Stenotrophomonas maltophilia	1	-
Prevotella bivia		1
Bacteroides spp	-	1
Burkholderia cepacia	-	1
Aspergillus strain	2	1

*: overlapping description, MRSA: Methicillin-resistant *Staphylococcus aureus*

Table 3 Empyema management, outcomes, and prognostic factors

Management and outcomes at first endpoint	ES group	Control group:	P values
mVATS (repeated)/mVATS indwell catheter (repeated)	3(1)/ 18(3)/7/(0)	0/0/ 26(4)/(5)	
/indwell catheter (repeated)/ (convert to surgical option)			
Catheter indwell periods (days)	12.3 ± 10.0	23.9 ± 19.7	p=0.0080
Parenteral antibiotic period (days)	10.2 ± 12.1	24.3 ± 20.2	p=0.0029
Febrile period (days)	2.4 ± 2.6	10.6 ± 9.8	p<0.001
CRP: post-week 1	6.6 ± 5.1	8.7 ± 7.0	p=0.2027
Residual pleural space: no/yes (unknown)	70/8	17/5(9)	p=0 .9519
Chest pain during management	none	none	
Disease cure: yes/no (curability %)	25/3 (89.3)	13/13 (50)	p=0.0016
Outcomes at second endpoint	**ES group**	**Control group:**	**P-values**
Hospital death: no/yes (mortality %)	24/4 (14.3)	15/11 (42.3)	p=0.0216
Hospital discharge: cured/died/suspended, convert	23/4/1(81.4)	11/10/5 (42.3)	p=0.0090
(Cured discharge rate %)			
Outcomes at third endpoint	**ES group**	**Control group:**	**P-values**
Disease recurrence: no/yes	23/2	13/1	p= 0.9237
Treatment: succeeded/failed (success rate %)	21/7 (75.0)	10/16 (38.5)	p=0.0060

CCS: Charlson comorbidity score, CRP: C-reactive protein, ES: electrolyzed saline, Mini VATS: video-as

Management and outcomes at the first end point

Most patients in the ES group had topical ES irrigation during mini VATS debridement with or without subsequent continuous catheter irrigation; seven patients had ES irrigation under indwelled catheter alone. In three patients with mental disturbance in the ES group, catheter indwelling for continuous irrigation and drainage was avoided in the mini VATS procedure. Four patients received repeated mini VATS for the incomplete removal of fibrin debris. None of the

Table 4 Multivariate analysis of prognostic factors by Cox proportional hazard model

Disease curability	p-values	hazard ratio	95% CI
Age (<=70/70<)	0.0342	3.8483	1.1058-13.3921
Comorbidity (CCS: 0/1, 2/3<)	0.2083	0.6460	0.3271-1.2758
Bronchopleural fistula (-/+)	0.0909	0.2392	0.0455-1.2558
Disease extension (local/total)	0.0059	0.3067	0.1323-0.7111
Residual dead space (no/yes)	0.9146	0.9694	0.5490-1.7116
Electrolyzed saline (+/-)	0.0022	0.3373	0.1685-0.6753
Mini VATS debridement (+/-)	0.0763	0.3705	0.1236-1.1106
Hospitalization rates	**p-values**	**hazard ratio**	**95% CI**
Age (<=70/70<)	0.9832	1.0111	0.3622-2.8226
Comorbidity (CCS: 0/1, 2/3<)	0.0063	0.3364	0.1539-0.735
Bronchopleural fistula (-/+)	0.1302	0.5072	0.2106-1.2217
Disease extension (local/total)	0.5175	1.756	0.3191-9.6652
Residual dead space (no/yes)	0.1595	0.6831	0.4016- 1.1618
Electrolyzed saline (+/-)	0.0179	0.4219	0.2065-0.8619
Mini VATS debridement (+/-)	0.6427	0.7703	0.2558-2.3198
Mid-term survival rates	**p-values**	**hazard ratio**	**95% CI**
Age (<=70/70<)	0.2574	0.5576	0.2029-1.5324
Comorbidity (CCS: 0/1, 2/3<)	0.0487	2.8371	1.0062-7.9995
Bronchopleural fistula (-/+)	0.0234	3.8882	1.2021-12.5763
Disease extension (local/total)	0.0897	0.3609	0.1113-1.1710
Residual dead space (no/yes)	0.0771	1.7160	0.9430-3.1226
Electrolyzed saline (+/-)	0.0102	3.2114	1.3178-7.8255
Mini VATS debridement (+/-)	0.1489	2.9113	0.6823-12.4216

CCS: Charlson comorbidity score, Mini VATS: video-assisted thoracoscopic surgery withminiaturized scopes under local anesthesia

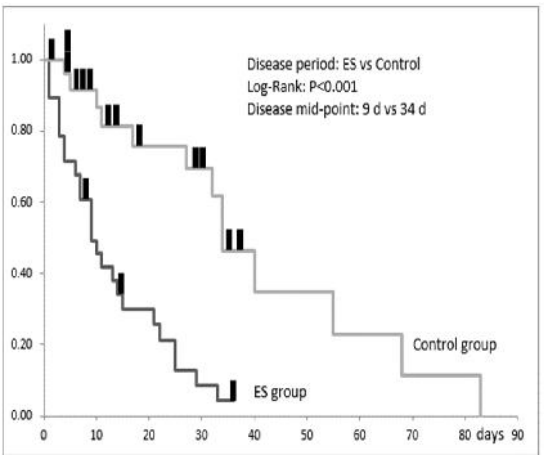

Figure 1 Empyema rate by management: Electrolyzed saline irrigation promptly curedempyema compared with conventional treatments. Electrolyzed saline group (disease mid-pointperiod: 9 days) versus Control group (disease mid-point period: 34 days). Solid pillars: patient death, suspended treatment, or conversion to surgical options.

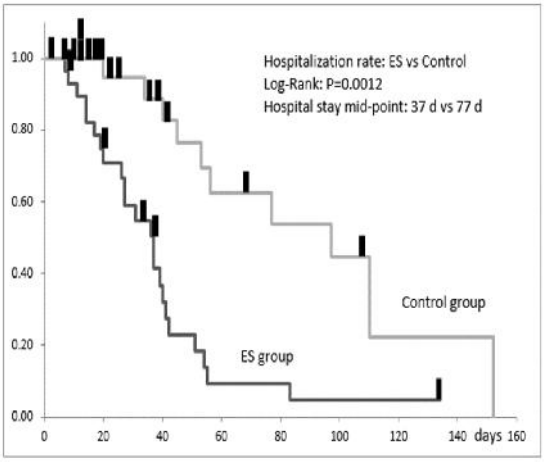

Figure 2 Hospital stay by management: The electrolyzed saline irrigation significantly shortened the hospital stay compared with conventional management. Electrolyzed saline group (hospital stay mid-point: 37 days) versus Control group (hospital stay mid-point: 77 days). Solid pillars: patient death, treatment suspension, or conversion to surgical options.

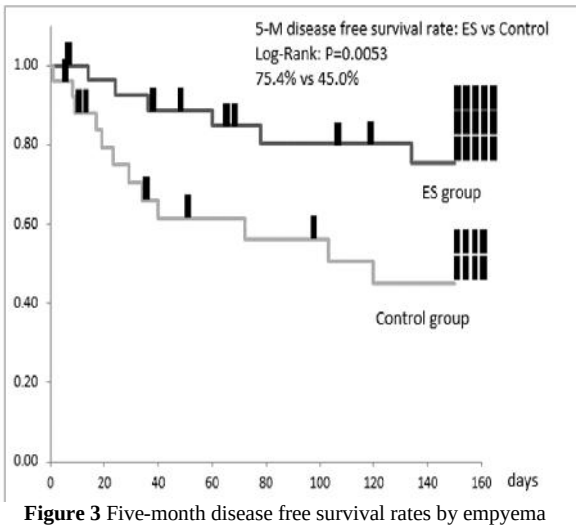

Figure 3 Five-month disease free survival rates by empyema management on Kaplan-MeierplotsThe electrolyzed saline irrigation significantly improved the survival rate compared with conventional management. Electrolyzed saline group (disease free survival rate at 5 months:75.4%) versus Control group (disease free survival rate at 5 months: 45.0%). Solid pillars:patient alive, lost to follow up, treatment suspension, or conversion to surgical options.

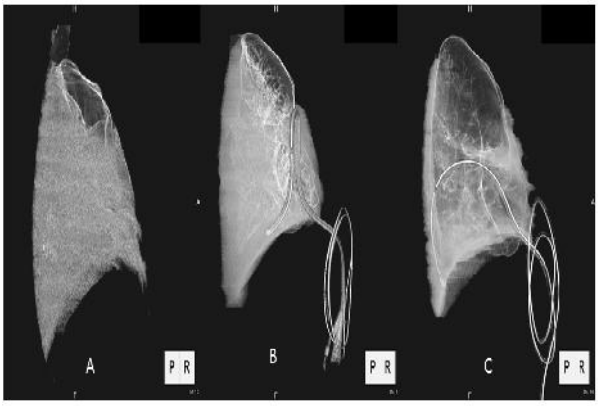

Figure 4 3-dimensional images of the right empyema space (A 76y.o. male with fibro-purulentempyema).A: Before catheter indwelling.
B: Multiple loculations disturbed uniform catheter irrigation and drainage.
C: Mini VATS debridement facilitated uniform irrigation and drainage with lung re-expansion.

patients in the ES group were converted to general anesthesia or invasive surgical options. All 26patients were treated with catheter indwelling in the Control group. Seven patients in the control group had physiological saline irrigation through an indwelled catheter, and the remaining nineteen patients had catheter drainage alone. Four of these patients had repeated catheter indwelling for insufficient pleural drainage. Five in the Control group were converted to surgical options of open thoracostomy, thoracotomic decortication, or closure of the bronchofistula with peri-cardiac fat pad. One patient in each group had suspended catheter management because of accidental removal. These two patients were followed by thoracentesis or parenteral antibiotics with refusal of catheter indwelling. The catheter indwelling interval in the ES group was significantly shorter than that in Control group. The duration of parenteral antibiotics after the treatment in the ES group was shorter than that in the Control group. Febrile above 37.0°C promptly diminished within a few days with improvements of other clinical features by the ES irrigation compared with the Control group. The level of CRP depression in post-ES irrigation was not significant because parenteral antibiotics were not principally administered after ES irrigation A quarter of the patients in both groups had prolonged residual pleural space after management for post-pneumonectomy space, bronchopleural fistula, or dense thickened pleura. No adverse effects, such as chest pain or abnormal hematologic examination results, were observed during ES irrigation. All patients, except 3 who died or had the indwell catheter suspended, in the ES group achieved elimination of bacterial colonization (Table3).Twenty-five patients in the ES group achieved cure of empyema (89.3%), and 13in the Control group were cured (50%). ES irrigation significantly improved disease curability in prompt intervals.
The disease mid-point in the ES group was 9days, while that in Control group was 34days on Kaplan-Meier plots (Figure 1).

Outcomes at second and third end point

Hospital length of stay was significantly shortened and hospital mortality was significantly decreased in the ES group compared with the Control Group. Hospitalization mid-points in the ES and Control groups were 37days and 77days, respectively (Table 3, Figure 2).There were two deaths from persistent empyema and acute respiratory distress syndrome (ARDS) caused by pneumonia during treatment procedures in the ES group. The most frequent cause of death in the Control group was ARDS. The probability of disease free survival rate at 5months in the ES group was 75.4%, while that in Control group was 45.0% (Figure 3). Two patients in the ES group had disease recurrence in the residual pleural space because of residual pathogens at the closed drainage port on catheter removal or residual bronchopleural fistula (Table3).

Multivariate analysis of disease prognosis

ES irrigation, age, and disease extension were significant contributors for disease curability. Mini VATS debridement was suggested to contribute to disease cure, but was not significant. Comorbidity and ES irrigation were significant effectors for length of hospital stay. ES irrigation, bronchofistula and CCS were significant contributors for mid-phase prognosis. A patient with fungus empyema and mild bronchofistula in the ES group achieved elimination of fungus colonization, but suddenly died from ARDS after hospital discharge. This patient was a candidate for surgical closure of bronchofistula, but her performance status did not allow for invasive procedures (Table 4).

Comment

The main treatment for empyema is the cleansing and closure of the pleural cavity for diminishing bacterial colonization[2-4]. Residual microbes and multiple loculations with massive purulent fibrin debris disturb this principle treatment, and the current conservative treatment with intravenous antibiotics and catheter drainage is frequently replaced by an invasive procedure with a long-term treatment period. A novel effective and less invasive approach has been required to resolve these problems[3]. ES solution is a novel general-purpose disinfectant for biological tissues, medical instruments, foods, and environmental sanitation[6, 9,10]. ES solution is generated by the simple process of salt water electrolysis. Hypochlorous acid contained in ES solution is considered as the main disinfectant[11]. Several Japanese companies succeeded in inventing electrolysis generators for ES solution in the late of 1980s[6]. ES aqueous solution became attractive for hospital sanitation when MRSA became the focus of hospital infections in the mid of 1990s[10,12]. ES has rapid effects against a broad

spectrum of pathogens, including spores, fungi, viruses, acid-fast bacilli, and MRSA, within a minute [10]. The bactericidal activity of ES is similar to that of 80% ethanol and superior to chlorhexidine and povidone iodine[6,9,13]. It tastes and smells of chlorine slightly stronger than municipal tap water. The chlorine smell is the sign of bactericidal activity in ES solution. One of our authors primarily applied ES solution for hospital sanitation of patient wards contaminated with MRSA since1992, and subsequently for open thoracostomy and necrotizing mediastinitis[6]. The bactericidal activity of the ES solution achieved prompt elimination of bacterial colonization and promoted healthy epithelialization of the pleural surface[6]. We have applied ES solution to the closed-space irrigation of acute empyema based on these findings since 2006[6].

Removal of fibrin debris under mini VATS as an alternative to intrapleural fibrinolytic therapy[14]facilitated uniform irrigation and drainage of the empyema space (Figure 4).

Total empyema sometimes disturbs complete removal of fibrin debris under mini VATS debridement and requires repeated mini VATS for removal of residual fibrin sludge. Mediastinal sites, inter-lobar space, or cost-phrenic angles in empyema pockets retain mass fibrin debris. Continuous ES irrigation under low-pressure suction promoted rapid disinfection and epithelialization of purulent space followed by spontaneous closureof the dead space. Single topical ES irrigation may be effective even when continuous catheter indwelling should be avoided. The principle goal of empyema treatment is closure of the dead space[2,3]. However, the findings in our patient with infection of the post-pneumonectomy space and other patients with residual dead space suggested that the closure of the empyema space may be unnecessary if disinfection of the pleura is achieved. The post-pneumonectomy patient had clear epithelialization of the pleural surface on the second

miniVATS and clear fluid with negative microbes on follow-up thoracentesis. One of the patients with residual dead space in ES group had disease relapse. Residual pathogens in the sludge of drainage port closed on catheter removal progressed again to the cleansed dead space. This patient had fermented gas and new niveau formation on follow-up chest X-ray. The residual sludge in the port could be flashed out by Valalva maneuvers on catheter removal and the port wound should be open with coverage by sealing film. Our former experiences prohibited ES irrigation for patients with bronchofistula, but the present study allowed its application to patients with mild symptoms of bronchofistula. The bactericidal activity of ES for disease cure was independent from patient performance status. However, bronchopleural fistula was another risk factor for poor mid-phase prognosis as well as comorbidity scores. If the patient's performance status allows, surgical options to close the fistula should be considered after the achievement of disease cure by ES irrigation. We achieved an89.3% curative rate of empyema with hospitalization mid-point of 37days and an 8% recurrence rate by ES irrigation. These results were significantly superior to those of conventional managements. The hospital stay in this series is longer for sociomedical reasons. A study of pleural space infection reported that non-operative patients exhibited 16.6% 30-day mortality, 30.1% discharge to an institutional care facility with an average hospital stay of 13 days, and 5.9% re-admission[15]. A study of fibropurulent empyema treated by VATS evacuation and/or decortication with postoperative drainage under general anesthesia reported an 85% success rate[16]. Our results of a less invasive approach by ES irrigation are superior to these historical controls, thus this approach may take the place of aggressive surgical approaches for acute empyema except bronchopleural fistula. We have experienced some limitations of ES solution in other treatments for postoperative empyema of lung resection. The epithelization of the necrotic stump of the bronchi or pulmonary arteries was not improved by use of ES solution while those of pulmonary veins were facilitated for granulations. High airway or arterial pressure may disturb the granulation of the necrotic stump.

ES solution has no adverse effects on the human body. It has been demonstrated to be non-toxic on biological tissues[12]. It is also gentle to the environment as it is instantly converted to ordinary water. The preparation of ES solution does not require a sterilization process and the cost of producing ES is quite low, US$0.25 for 50 liters/day of the solution[17]. Current disinfectants, ethanol is a stimulant to wounds and is flammable, chlorhexidine does not have strong bactericidal activity, and povidone iodine risks iodine intoxication by massive or prolonged use. Our ongoing projects with ES solution are for general purpose disinfection or prophylaxis for surgical sites, traumatic wounds, closed space infections, medical instruments, or hospital sanitations, alternative to conventional disinfectants procedures. ES solution had long term bactericidal activity above a few months if it was stored in dark rooms. ES solution is now easily applicable even in field hospitals or clinics at disaster sites or refugee camps. Study Limitations There are several limitations in this study. The study population is still small for analyzing prognostic factors, such as management procedures, which may give a potential bias. Mini VATS debridement alone may contribute to the results of empyema treatment, and the comparison between mini VATS alone and mini VATS with ES irrigation should be tested. This conservative and radical approach for empyema will be discussed in future larger cohort studies.

In summary, empyema without bronchofistula is now a well controllable disease by intrapleural irrigation with electrolyzed saline.

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