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Comparison of Video-Assisted Thoracoscopic Surgery and Intrapleural Urokinase as an Initial Treatment for Parapneumonic Effusion and Thoracic Empyema

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ABSTRACT

Introduction: The treatment of complicated parapneumonic effusion (PPE) and thoracic empyema (TE) is controversial; and the choice of treatment after confirming the failure of simple drainage remains unclear. The purpose of this study was to compare the outcomes of intrapleural urokinase (UK) administration and video-assisted thoracoscopic surgery (VATS) as initial treatment options for PPE and TE.
Materials and Methods: We retrospectively reviewed and compared the data of 20 patients with PPE and TE diagnosed between January 2010 and December 2012 at our hospital, dividing them on the basis of the initial treatment into a video-assisted thoracoscopic surgery (VATS) group (n=9) and UK group (n=11).
Results: Age was the only statistically different parameter between both groups (*P*=0.025); with the mean age of the VATS and UK groups being 64 and 76 years, respectively. There was no significant difference in the duration of drainage or success rate between the UK or VATS groups. Although no statistically significant differences (*P*=0.20) were observed, duration of hospital stay was longer in the UK group (21 and 28 day for VATS and UK, respectively).
Conclusion: VATS for PPE and TE may shorten the duration of hospital stay. However, UK administration may be used for selective patients because it is considered to yield outcomes similar to VATS.

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Introduction

Intrapleural fibrinolytic therapy and video-assisted thoracoscopic surgery (VATS) are the initial treatment options for complicated parapneumonic effusion (PPE) and acute thoracic empyema (TE). VATS is an effective initial treatment for PPE or TE, with a success rate of 80-90% (1-3). Despite the high success rate of VATS, patients with PPE or TE tend to posses poor risk to become surgical canditates. On the other hand, intrapleural fibrinolytic therapy may be an alternative therapy though it is stated in the Cochrane Database Review that it should be considered as an adjunctive therapy and routine use is not recommended because of the low power of the studies examining its efficacy (4). Thus because of lack of the evidence, it is unclear which intervention is the most appropriate in these conditions. This study compared the outcomes of intrapleural urokinase (UK) administration and VATS as initial treatment options for PPE and TE and identified the advantages of each intervention.

Materials and Methods

The study protocol was approved by the Review Board of National Hospital Organization

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Table 1. Characteristics of Two Treatment Groups

Variables	All patients (n=20)	VATS (n=9)	UK (n=11)	*P*-value
Age, yr	70.4±10.2	64.1±7.0	75.5±9.8	0.027
Male/Female	17/3	8/1	9/2	1
Right/left side	13/7	5/4	8/3	0.64
Associated diseases other than pneumonia	11 (55%)	4 (44%)	7 (64%)	0.65
VATS or UK from the onset, day	7.5±3.8	8.1±4.0	6.9±3.7	0.65
ACCP category 3/4	16/4	8/1	8/3	0.59
Performance Status 0-1/2-3	15/5	7/2	8/3	1
WBC, x10³/μl	19.4±9.5	23.1±11.4	16.4±6.6	0.17
CRP, mg/dl	23.4±9.0	25.6±10.1	21.5±7.3	0.25
LDH level of pleural fluid, U/l	3390±6290	1990±1520	4350±8130	0.86
Glucose level of pleural fluid, ml/dl	66±60	63±65	64±58	0.9
Positive culture	4(20%)	1(11%)	3(27%)	0.59

VATS=Video-assisted Thoracoscopic Surgery, UK=Urokinase, ACCP=American College of Chest Physicians, WBC=white blood cell count, CRP= C-reacting protein, LDH=lactate dehydrogenase

Table 2. Associated disease

Variables	VATS (n=4)	UK (n=7)
COPD	0	3
Cardiovascular	1	1
Stroke	2	3
Diabetes	1	1
SAS	1	0

COPD, choronic obstructive disease, SAS, sleep apnea syndrome

Ehime Medical Center, and the written informed consent was waived because our study was retrospective in design. Decisions regarding the treatment options were made by the surgeons and the physicians in the institution. Surgically-treated and UK-treated cases admitted to the hospital between January 2010 and December 2012 were reviewed. Chest X-ray, CT, and pleural fluid chemistry and bacteriology were evaluated. Patients who fulfilled Categories 3 or 4 of the American College of Chest Physicians (ACCP), Categorizing Risk for Poor Outcome in Patients with PPE (5) were identified. A case of chronic empyema due to tuberculosis was excluded from the study.

After a simple thoracic drainage or thoracentesis, the patients were divided into two groups on the basis of their initial treatment (VATS or UK group). Patient backgrounds, duration of chest tube drainage, duration of hospital stay, need for alternative treatments, and recurrence were reviewed.

In the VATS group, the procedures were performed under general anesthesia and one-lung ventilation for all cases. Two or three trocars were placed for a thoracoscope or other instruments. The loculated cavity was disrupted, fibrous adhesions were separated, and pleural debris were removed. A chest drain was placed through the ports using a negative suction pressure of 10 cm of H_2O.

In the UK group, urokinase was diluted to 100 ml in normal saline and administered at a dose of 60,000 or 120,000 U through a percutaneous chest drain. After UK administration, the drain was clamped for 2–3 h, then unclamped, followed by administration of 500 ml of normal saline. When the drain was unclamped, it was maintained under a negative suction pressure of 5–15 cm of H_2O until the next administration. This process was repeated at intervals of approximately 24 h. The duration of treatment was determined on the basis of the patient's response.

In both interventions, the chest drain was removed when the discharge was less than 100 ml/24 h and macroscopically serous.

Statistical analysis

The results were expressed as mean ± standard deviation. GraphPad Prism 5 (Graphpad Software, Inc., San Diego, California) was used to perform statistical procedures. The baseline characteristics and outcomes were compared using the Mann–Whitney U test and Fisher's exact test where appropriate. $P \leq 0.05$ was considered statistically significant.

Results

Sixteen cases (80%) of PPE and 4 cases (20%) of TE were treated with intrapleural UK or VATS during the review period. No patient had postsurgical or bronchopleural fistulae. Nine cases (45%) underwent VATS and 11 (55%) received UK as a primary interventions.

Comparison between both groups at the start of VATS or UK administration is shown in Table 1. Patient age was the only significant different factor between both groups (P=0.025). Pleural fluid cultures showed a streptococcus anginosus infection in a patient in the VATS group and three anaerobic bacterial infections in the UK group. Peripheral white blood cell counts and serum C-reactive protein levels were higher in the VATS group than the UK group, although these differences were not statistically significant (P=0.17 and 0.25, respectively).

Associated diseases other than pneumonia or other well-controlled diseases are shown in Table 2. One case (11%) of percutaneous coronary intervention for myocardial infarction, one case (11%) of sleep apnea syndrome (SAS), and two

Table 3. Outcome of Two Treatment Groups

	VATS (n=9)	UK (n=11)	*P* Value
Drainage, day	11±7	10±5	0.85
Hospital stay, day	21±7	28±13	0.2
Follow up, week	75±49	77±27	0.82
Success/Failure	8/1	10/1	1.0

VATS=Video-assisted Thoracoscopic Surgery, UK=Urokinase

cases (22%) of hemiplegia due to cerebral infarctions were identified in the VATS group. Three cases (27%) of chronic obstructive pulmonary diseases, one case (9%) of arrhythmia requiring medication, and three cases (27%) of a past history of cerebral infarction, including one case (9%) of hemiplegia, were identified in the UK group. Poorly-controlled diabetes was identified in one patient from each group (11% and 9% for VATS and UK group, respectively).

The mean time required for VATS was 127±43 min, with bleeding volume including effusion or pus being 388±357 ml. No major intraoperative complications were noted. The patient with SAS required overnight mechanical ventilation for respiratory failure, while another patient required an intrapleural UK instillation for an intrapleural hematoma one day after VATS.

UK was administered 1–5 times (mean, 3 times) using the protocol described above. No adverse events such as local pleural or systemic hemorrhage or chest pain were observed in any patient.

The outcomes in the two groups are compared in Table 3. No patient in either group died in hospital or within 30 postoperative days. The duration of drainage was not significantly different between the two groups. Duration of hospital stay was shorter in the VATS group than the UK group, although this difference was not statistically significant (P=0.20). The initial treatment failure was seen in one case from each group; the case in the VATS group relapsed 3 months after the first intervention and required drainage and another case in the UK group required VATS for a residual undrained cavity after the intrapleural administrations. In the latter case, UK administrations were repeated three times, and CT showed large amounts of loculated fluid remaining in the cavity.

Discussion

The success rate in VATS for PPE or TE in a recent large study (234 patients) reported by Luh *et al* (3) was 88%, similary close to the rate measured in present study. In our institution, if the patient is a good candidate, a decision for VATS treatment will be made as soon as the simple drainage was found to be insufficient. UK administration is chosen in cases with severe comorbities, those with a low performance status, or those requiring conservative treatment.

VATS as an initial treatment may shorten the duration of hospital stay in patients with PPE or TE. We showed that the duration of hospital stay in the VATS group tended to be shorter than that in the UK group. Because the patients were not randomized, the baseline characteristics of the patients, particularly age, in the two groups were not the same. Although the VATS group had higher levels of inflammatory markers than the UK group, the mean duration of hospital stay in the VATS group tended to be shorter than that in the UK group. However, the sample size in our study may have been too small to detect the differences in the duration of hospital stay, and a study with a larger sample size is necessary to confirm the benefits of VATS.

In previous prospective studies for intra-pleural fibrinolytic therapy, streptokinase was used as the fibrinolytic agent and proved to be less effective than VATS; compared with normal saline, streptokinase failed to improve mortality, decrease the need for surgery, or shorten the duration of hospital stay (1, 6). The difference between these studies and the present study are the use of UK as a fibrinolytic agent and the use of normal saline after administration of the fibrinolytic agent. In our study, the success rate of the primary intervention in the UK group was similar to VATS group. It suggests that UK administration may be an alternative intervention for PPE or TE patients requiring conservative treatment.

More recently, some studies have used tissue plasminogen activator (tPA) and referred to the efficacy of this agent in PPE and TE (7, 8). tPA was shown to be effective as a conservative treatment for PPE and TE; however, the high cost of the drug was a problem. In Japan, a single therapeutic dose of tPA costs approximately 10 times more than that of UK. Furthermore, streptokinase is not commercially available in Japan; therefore, UK is the only fibrinolytic agent currently used in Japan.

The present study showed that hospital costs were lower in the UK group than in the VATS group (data not shown). There is limited evidence on the cost of PPE and TE treatment in adult patients. Cohen and co-workers reported that the cost of the chest tube and administration of fibrinolytics in pediatric empyema was $7,787, which was considerably less than the cost of VATS ($17,874), repeated thoracentesis ($18, 580), or other treatment options (9). The hospital costs in our VATS group were approximately twice as high as that in the UK group (approximately 1,770,000 vs. 800,000 JPY).

This study suggested that the choice of VATS in PPE or TE may shorten the duration of hospital stay. However, because VATS and UK have

similar clinical outcomes, we recommend that UK administration may be an appropriate alternative in patients requiring conservative treatment. Because the current study had a retrospective design and a relatively small sample size, it did not provide definitive conclusions regarding which intervention is the best initial treatment option. Therefore, prospective studies or studies with larger sample sizes are necessary to clarify this question.

Conclusion

With regard to treatment of PPE or TE, VATS may shorten the duration of hospital stay, whereas UK administration may be an alternative option, considering its clinical outcomes and cost-effectiveness.

Conflict of Interest

All the authors have declared no competing interest.

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