Kirurške možnosti zdravljenja malignih plevralnih izlivov karcinoma dojke Primerjava metod

Surgical options for treating malignant pleural effusion in patients with breast carcinoma Comparison of methods

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Izvleček

Izhodišča: Pogost zaplet karcinoma dojke je ponavljajoči se maligni plevralni izliv (MPI), ki povzroča bolnicam zaradi pritiska na pljuča dihalne težave, dražeč kašelj in bolečine. Ker pri približno polovici bolnic s plevralnim izlivom le tega ne moremo sanirati s sistemskim zdravljenjem, uporabimo enega od načinov blažilnega zdravljenja, v zadnjem času najpogosteje s kemično plevrodezo s talkom (KPT) ali torakoskopsko mehansko plevrodezo (TMP). V študiji smo želeli dokazati določene prednosti TMP, predvsem pri nižjih vrednostih pH MPI, ko KPT ne daje zadovoljivih rezultatov.

Metode: V prospektivno randomizirano raziskavo smo vključili 87 bolnic s karcinomom dojke in z morfološko potrjenim MPI. Bolnice smo razporedili v dve skupini glede na vrsto blažilnega posega: skupino TMP (torakoskopska mehanska plevrodeza) in skupino KPT (kemična plevrodeza s talkom) ter štiri podskupine glede na vrednosti pH MPI (≥ 7,3; < 7,3).

Rezultati: Uspešnost (brez ponovitve MPI) KPT (91 %) in TMP (92 %) je bila pri bolnicah z vrednostjo pH MPI nad 7,3 identična. Pri bolnicah z vrednostjo pH pod 7,3 pa je bila TMP uspešnejša metoda (81 %) kot KPT (55 %). Najnižji vrednosti pH MPI, pri katerih sta bili metodi še uspešni, sta bili 7,06 pri TMP in 7,25 pri KPT.

Zaključki: Pri vrednostih pH MPI nad 7,3 je KPT zaradi svoje enostavnosti uporabnejša blažilna metoda. TMP, ki je uspešnejša pri nižjih vrednostih pH, pa ima tudi v skupini bolnic z višjimi vrednostmi pH svoje nesporno mesto, predvsem pri reševanju citološko ali histološko nepotrjenih MPI in pri sumu na zarastline v plevralnem prostoru.

Abstract

Background: Recurrent malignant pleural effusion (MPE) is a common complication of breast carcinoma causing an irritating cough and pain due to the fluid exerting pressure on the lungs. As the systemic therapy fails in approximately half of the patients with pleural effusion, one of the palliative methods is used. Lately, the most commonly used procedure is the chemical pleurodesis with talc or the thoracoscopic mechanical pleurodesis. The aim of the study was to prove certain advantages of the latter method, especially at lower MPE pH values, since the chemical pleurodesis in those cases does not provide acceptable results.

Methods: This prospective, randomized study included 87 patients with breast carcinoma and morphologically proven malignant pleural effusion. Patients were divided into two groups according to palliative treatment: the TMP group (thoracoscopic mechanical pleurodesis) and the TP group (talc pleurodesis). There were also four subcategories according to the pH value of malignant pleural effusion (≥ 7.3, < 7.3).

Results: The effectiveness (no recurrence of pleural effusion) of TP (91 %) and TMP (92 %) was identical in patients with a MPE pH value above 7.3. However, in patients with pH value under 7.3 TMP was more successful (81 %) than TP (55 %). The lowest pH values at which the methods proved successful were 7.06 in TMP and 7.25 in TP.

Conclusion: TP proved to be a more useful palliative method in patients with pH values above 7.3 due to its simplicity. On the other hand, TMP is more successful at lower pH values. Furthermore, TMP is also very effective in the group of patients with higher pH values, especially for handling cytologically or histologically unconfirmed malignant pleural effusions and in suspected adhesions in the pleural space.

Introduction

MPE, which is the result of an advanced underlying disease, can be caused by different carcinomas[1,2]. Pulmonary carcinoma, breast carcinoma, and lymphoma are responsible for the incidence of two thirds of MPE. Approximately 25 % of patients with pulmonary carcinoma and 35 % of patients with malignant lymphoma develop MPE during their illness[3]. Approximately 50 % of women with breast carcinoma develop MPE during their illness[4]. In thoracic, gastric, urological, and ovarian carcinoma, survival is limited to only a few weeks or months[5]. MPE in women with breast carcinoma does not indicate a terminal phase of illness as their survival can be months or years after a successfully treated effusion[1]. As MPE causes additional problems to patients who already suffer from an underlying disease, it is necessary to employ a suitable palliative treatment of effusion when symptomatic therapy fails.

Pathogenesis of malignant pleural effusion

Pleural fluid accumulation in the pleural space occurs due to impaired lymphatic drainage, i.e. tumour or metastasis blockade, increased capillary permeability, inflammatory response or capillary endothelial damage and direct tumour or metastatic infiltration of the pleural space[3]. Pleural metastases usually develop in the visceral pleura resulting from pulmonary embolism and spread to the parietal pleura through the pleural fluid or adhesions which were already present in the pleural space or developed due to tumour stimulus[6,7].

MPE can also be caused by other factors, such as hypoalbuminemia, enhanced capillary permeability due to the toxic effect of a tumour on endothelial cells, production of vasoactive peptides[8] and transforming growth factor (TGF-ß) produced by different tumour cells, which can lead to apoptosis[9].

MPE are mostly exudates with a protein concentration level around 40 g/l and a ratio between LDH concentration in the pleural fluid and plasma higher than 0.6[10], and rarely transudates. They can be either serous or mixed with bigger or smaller amount of blood. Serous exudates develop due to obstruction of lymphatic drainage or pulmonary atelectasis, while blood exudates are due to direct tumour infiltration of the pleural space or tumour-induced angiogenesis and increased vascular permeability. In most cases, blood in pleural effusion without reported thoracic injury indicates the presence of a malignant tumour[1].

The normal pH of pleural fluid is around 7.4. Approximately one third of MPE have a pH below 7.3 and lower glucose concentration (below 0.6 g/L)[1,10]. Lower pH results from impaired transport of end products of glucose metabolism in the pleural fluid through altered malignant or fibrotic pleura[1,11,12]. Lactate and CO_2 are produced during glucose metabolism in the pleural fluid and due to impaired transport through altered and thickened pleura, accumulation of protons in the pleural fluid and consequently lower pH value occur[11]. Effusions with a low pH are associated with patients' lower survival rate[5].

Aims of palliative treatment

The purpose of palliative treatment is to relieve respiratory distress, which can be achieved with complete and permanent termination of MPE and with minimal surgical morbidity. Eliminating MPE does not treat the underlying malignant disease but improves the quality of life on account of improved respiratory functions.

When choosing a certain palliative intervention for treating MPE, patient's general condition, rate of pleural fluid accumulation, stage of the underlying disease and expected survival need to be considered.

Mechanism and effectiveness of palliative methods (TMP, TP)

Chemical pleurodesis: it uses talc sterilized with heat or gamma rays. Individual talc particles should not exceed the size of 10 µm[13]. After the talc solution is insufflated into the pleural space, acute inflammatory

response occurs in layers of mesothelial cells of the parietal and visceral pleura with fibroblast proliferation, macrophage infiltration, foreign body reaction, decreased levels of fibrinolysis reactions and consequent pleurodesis[13,14]. The talc solution is insufflated through a thoracic catheter after malignant pleural effusion has been drained or by means of a thoracoscope under general anaesthesia.

The success of the mentioned palliative procedure is around 90 %[15,16,17], however, certain authors discourage from using talc due to possible anaphylactic reactions, pains, embolisms, hemiplegias, or respiratory failures[18]. In MPE pH values lower than 7.3 the success of TP is significantly reduced because in the pleura altered due to carcinoma or fibrosis the sclerosing agent does not provoke a strong enough inflammatory response or fibroplasia[6,14].

Thoracoscopic mechanical pleurodesis: After scarification of the visceral and parietal pleura, petechial bleeding is induced and inflammatory response develops on pleural surface as a specific form of reaction of vascularized connective tissue. The inflammatory response is closely related with reparation reaction resulting from the activity of inflammatory cause. In the reparation process, the damaged tissue is either replaced with parenchyma cells of the same phenotype or the defect is overgrown by connective tissue (scar) (Figure 1). Reparation is usually a combination of both mentioned processes[19] (Figure 2). TMP, which has not been mentioned in foreign professional literature as a palliative method of treating malignant pleural effusions, proved in our previous study[20] to be successful in dealing with this additional pathology (93.2 % without recurrence of pleural effusion).

Methods

The prospective randomized study included 87 patients with breast carcinoma and a resulting morphologically confirmed MPE resistant to systemic treatment, who were hospitalized at the Department of Thoracic Surgery of University Medical Centre Maribor between June 1996 and June 2003. The patients were divided into two large groups by the type of palliative intervention employed for treating MPE: TMP group (thoracoscopic mechanical pleurodesis) and TP group (talc pleurodesis). Patients in each group were further divided into subgroups by MPE pH values obtained by pleural puncture to relieve pressure. We excluded patients who were not fit to undergo a surgical procedure under general anaesthesia due to primary or accompanying diseases (9 patients). The patients did not receive any postoperative chemotherapy or radiotherapy; they received only symptomatic therapy. Randomization was performed using the sealed envelope method stating the group the patient belongs to. All patients were informed about the course of the study and gave their written consent to participation. The study was approved by the National Medical Ethics Committee of the Republic of Slovenia.

Before the palliative procedure, we performed a pleural puncture in all patients and sent a fluid sample to the laboratory for pH measurement and cytological and biochemical analyses. To exclude errors in pH values that may occur during transport to the laboratory, samples were taken under sterile conditions and transported in heparinised syringes on ice. pH values were determined within 1 h after sampling in a manner analogous to that for arterial pH values by using a blood gas analyser (AVL 990).

The following data were collected from the patients:

1. recurrence of pleural effusion after 1 day, 1 week, 1 month, 3 months, and 6 months, (signs of pleural effusion on conventional and/or lateral decubitus radiographs),
2. the lowest value of MPE pH at which the methods were still effective,
3. complications after individual treatments,
4. perioperative mortality.

The following was used for statistical analysis: t test, χ^2 test, logical regression and multiple linear regression. The statistical significance threshold was set at $P < 0.05$.

Table 1: Recurrence of MPE in patients, divided by subgroups according to pleural effusion pH value

	TMP TMP		TP KPT	
Recurrence of malignant pleural effusion after:	Subgroup 1 pH≥ 7.3 24 patients number (%)	Subgroup 3 pH< 7.3 21 patients number (%)	Subgroup 2 pH≥ 7.3 22 patients number (%)	Subgroup 4 pH< 7.3 20 patients number (%)
1 day	0	3 (14 %)	1 (4.5 %)	6 (30 %)
1 week	1 (4 %)	4 (19 %)	2 (9 %)	9 (45 %)
1 month	1 (4 %)	4 (19 %)	2 (9 %)	9 (45 %)
3 months	2 (8 %)	4 (19 %)	2 (9 %)	9 (45 %)
6 months	2 (8 %)	4 (19 %)	2 (9 %)	9 (45 %)

TMP–thoracoscopic mechanical pleurodesis; TP- talc pleurodesis.

Surgical palliative methods

Talc pleurodesis (TP) Patients treated by TP had a chest tube inserted through the fifth or sixth intercostal space in the mid axilliary line under local anaesthesia. Five grams of sterile talc dissolved in 100 ml of physiological solution were insufflated. Patients were given 100 mg of pethidine an hour before the procedure. After the procedure, the patients had chest tube drainage inserted. The drain was removed when drainage was below 100 ml over 24 h.

Thoracoscopic mechanical pleurodesis (TMP) TMP was performed utilising general anaesthesia with double lumen orotracheal intubation allowing for ipsilateral lung collapse. Patients were placed in a lateral decubitus position as for posterolateral thoracotomy. The trocar for thoracoscope was inserted through two or maximum three intercostal spaces with up to 2 centimetres in length for the optic portal and one or two working portals. A thorough inspection of the pleural cavity, lysis of possible adhesions (to ensure lung expansion) and biopsy of suspected areas were performed prior to pleurodesis. This was followed by scarification of the parietal and visceral pleura to induce petechial bleeding, resulting in a diffuse inflammatory response and fibroplasia. Inflammatory response is closely related with reparation reaction resulting from the activity of inflammatory cause. In the reparation process, the damaged tissue is either replaced with parenchyma cells of the same phenotype or the defect is overgrown by connective tissue. Damage reparation is often a combination of both mentioned processes. After scarification, the anaesthesiologist administered artificial ventilation to ensure lung expansion. A few days after surgery, the patients had a chest tube inserted. The chest tube was removed when its drainage was below 100 ml over 24 h.

Results

1. Recurrence of malignant pleural effusion

Recurrence of MPE of all 87 patients treated by TMP and TP after one day, one week, one month, three and six months is demonstrated in Table 1.

Recurrence of MPE after 6 months was proved in two patients from Subgroup 1 and four patients from Subgroup 3, while in the same period recurrence of MPE was proved in four patients from Subgroup 2 and nine patients from Subgroup 4. While TMP and TP were equally successful in patients with pH levels above 7.3 (92 % and 91 %), a significant difference occurred in patients with pH levels below 7.3 (81 % and 55 %) (p=0.07).

Table 2: Number of complications and perioperative mortality in subgroups.

	TMP		TP	
	Subgroup 1 pH≥7.3 24 patients number (%)	Subgroup 3 pH<7.3 21 patients number (%)	Subgroup 2 pH≥7.3 22 patients number(%)	Subgroup 4 pH<7.3 20 patients number (%)
Complications	4 (16 %)	3 (14 %)	4 (18 %)	7 (35 %)
Perioperative mortality	0	0	2 (9 %)	2 (10 %)

TMP–thoracoscopic mechanical pleurodesis; TP- talc pleurodesis.

2. The lowest pH value of pleural fluid at which the methods were still successful

The lowest pH value of pleural fluid at which the methods were still successful was 7.06 in TMP group and 7.25 in TP group.

3. Number of complications and perioperative mortality

The difference in the number of postoperative complications in TMP (7 complications) and TP group (11 complications) was not statistically significant ($p = 0.221$) (Table 2). However, complications in TMP group were easier to handle. This group of patients had three cases of longer air leakage in the chest tube and one case of significant bleeding handled with blood transfusion and no operative hemostasis was necessary, one case of subcutaneous emphysema, and two cases of wound inflammation. The most frequent complication in TP group was wound inflammation in chest tube drainage (in eight patients), which was associated with longer drainage, two patients had subcutaneous emphysema, and one developed bronchopleural fistula.

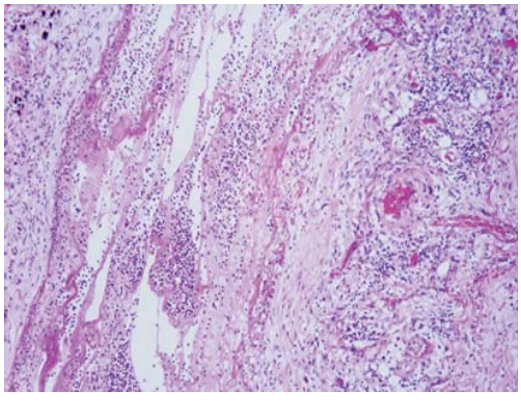

Figure 1: Microscopic demonstration of scarred tissue between the parietal and visceral pleura after thoracoscopic mechanical pleurodesis

There was no case of perioperative mortality reported in TMP group (30 days after the operative procedure). In TP group, two patients died from pulmonary embolism, one due to myocardial infarction and one due to sepsis. The difference between groups was statistically significant ($p = 0.034$) (Table 2).

Discussion

MPE represents a serious medical problem owing to its frequent occurrence and its treatment is often associated with failures and numerous complications. As patients suffer from the primary disease while MPE causes serious additional respiratory distress, irritating cough and pain by exerting pressure on the lungs, it is necessary to employ a palliative procedure to prevent fluid accumulation when systemic therapy fails to control MPE, despite the fact that MPE indicates a progression of the primary malignant disease and limits the patient's survival to a few months. The purpose of palliative treatment is to improve the quality of patients' remaining life, whereby different palliative procedures are employed regarding the patient's general condition, expected survival and rate of pleural fluid accumulation. TP is used most of the time, but its success rate decreases in MPE pH values < 7.3.

The purpose of our study is to determine whether a palliative method is more successful in lower MPE pH than TP and the lowest pH where TMP and TP are still successful.

TP, which is insufflated into the pleural space with chest tube drainage or controlled by means of thoracoscopy[21,22,23], is, according to different authors, successful in treating malignant pleural effusions in breast

carcinoma in 85 % to 95 % of cases[24,25]. The results of our study were identical as the success of TP in the subgroup of patients with a pH value ≥ 7.3 amounted to 91 %. In the subgroup of patients with a pH value < 7.3, the success of TP was only 55 %, which corresponds to reports of different authors stating that the success of TP is significantly decreased in treating malignant pleural effusions with low pH values[6].

TMP was successful in the subgroup of patients with pH values ≥ 7.3 (92 %) and comparable with TP (91 %). In the subgroup with MPE pH < 7.3 the success rate of TMP was 81 % and significantly higher than in TP (55 %) (p = 0.07). The study results have confirmed that TMP in lower pH values is more successful palliative method for treating recurrent MPE in breast carcinoma than TP, which confirms the basic hypothesis of our study.

The higher success rate of TMP, especially in treating MPE in breast carcinoma with lower pH (below 7.3) related to numerous fibrin and malignant changes on parietal and visceral pleura, is attributable to certain intraoperative procedures enabled by TMP. The first is good exposure of the entire pleural space and lung deflation on the side of the surgical procedure, which enables greater mobility of all the necessary instruments, easier access to all parts of pleural space and consequently easier collection of suspect materials for histological examination and easier performance of mechanical pleurodesis. Another important advantage is elimination of potential adhesions in the pleural space prior to abrasion of the parietal and visceral pleura, which is required for complete lung expansion after surgery. If fibrin plaques were discovered during thoracoscopic examination, which could affect lung expansion, we performed a thoracoscopic decortication (in five cases). After the procedure, the anaesthesiologist performed positive pressure ventilation to achieve a complete lung expansion required for successful pleurodesis or adhesion of the visceral or parietal pleura.

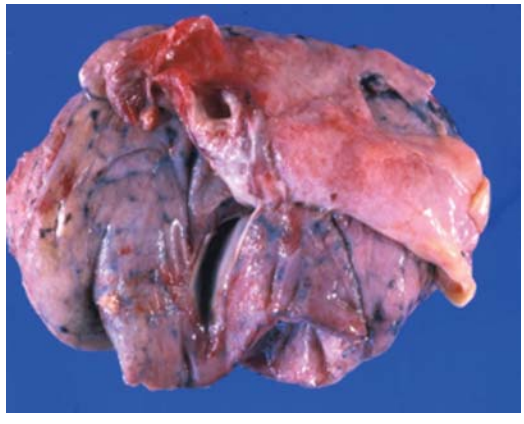

Figure 2: Pulmonary parenchyma and adhesion after thoracoscopic mechanical pleurodesis.

The lowest MPE pH values where the methods were still successful were 7.06 in TMP and 7.25 in TP. These results can also be associated with the advantages provided by TMP regarding the already mentioned cause of lower MPE pH.

Interesting data was obtained in studying the time of recurrence of MPE after a certain palliative intervention. In patients with a pH ≥ 7.3 there was no recurrence of pleural effusion on the first day after TMP, one recurrence after one week in one patient, and two after three months, which also remained the same after six months. In patients with a pH < 7.3, three patients were diagnosed with a massive visceral carcinoma during a thoracoscopic procedure and TMP was not possible. A recurrence of MPE was diagnosed after a week but later during check-up performed after one, three and six months there was no recurrence of MPE. In patients with a pH ≥ 7.3, a recurrence of MPE after TP was diagnosed after a day and two cases after a week. In patients with a pH < 7.3, MPE occurred in six cases after a day and in nine cases after a week. Analysis of the results showed that most recurrences were in all subgroups after TMP and TP the first day or week after the intervention. This indicated that the main reason for recurring MPE lies in unsuccessful mechanical or chemical pleurodesis or incomplete obliteration of the pleural space after mechanical or chemical pleurodesis.

The difference in the number of postoperative complications between TMP and TP was statistically significant (p=0.221). The majority of complications in both methods (longer ventilation by chest tube drainage, subcutaneous emphysema) was easily solved and is generally known in thoracic and thoracoscopic surgery. The only seri-

ous problems were more frequent wound inflammations in chest tube drainage in TP group (eight patients), which is associated with longer drainage use, while the most demanding complication in both groups (development of bronchopleural fistula in TP group) cannot be associated with the choice of surgical intervention. The comparison of our results and those of other authors is difficult as the majority report success of an individual method with smaller emphasis on complications. An important contribution was provided by Walter et al[18] who discourage from using talc due to possible anaphylactic reactions, pain, embolisms, hemiplegia, or respiratory failure. In our study, no postoperative mortality was reported in TMP group, while there were 4 cases in TP group. The difference was statistically significant ($p = 0.034$). As two patients died due to massive pulmonary embolism, one due to myocardial infarction and one due to sepsis, the causes of death, which are relatively frequent in oncologic surgery, can hardly be associated with possible complications of talc use. Based on our experiences, we can claim that TMP and TP are safe palliative methods for the treatment of recurrent MPE.

TMP, as a method for the treatment of recurrent MPE, was developed at the Department of Thoracic Surgery of University Medical Centre Maribor. We discussed its efficacy reported in foreign professional literature[20,26]. Numerous authors abroad mention it as a complementary or priority method for solving this complicated pathology[27]. We are interested in how the discussed treatment scheme could handle the problem of resulting MPE in primary carcinomas of other organs, which due to their frequent occurrence present an extensive medical problem. Regarding the known pathophysiology of malignant pleural effusions and their varying pH values, we consider TMP to provide satisfactory results also in treating other MPE with lower pH values.

This study has confirmed that altered MPE pH values in breast carcinoma affect the success of treating this effusion by TMP and TP and yielded the following conclusions, important for clinical practice:

- TMP is, in MPE pH values below 7.3, a more successful palliative method of treating MPE in breast carcinoma than previously used TP. As we have learned from professional literature that approximately 50 % of patients with breast carcinoma develop MPE during the disease and that around 30 % of patients have a PH value of pleural effusion below 7.3, we are able to relieve respiratory problems, irritating cough, and chest pain by TMP in a large number of patients and consequently improve the quality of their remaining life.
- TMP is not associated with an increased number of postoperative complications or higher mortality in comparison with the less aggressive TP.
- by defining the lowest MPE pH values in breast carcinoma where TMP was still successful, we have proved that its use is also sensible in lower pH values when TP is no longer effective.
- a great advantage of TMP is the possibility of thorough inspection of the pleural cavity and targeted sampling of tissues from suspected areas, good exposure of carcinoma process in the pleural cavity and relieving incarcerated fibrotic lungs. Another advantage is also greater possibility of lung expansion after pleurodesis with positive pressure ventilation.
- in pH values above 7.3, TP remains the basic palliative treatment method for MPE in breast carcinoma.

Conclusion

Despite the general applicability and simplicity of TP, TMP is nevertheless important in diagnosing and treating MPE and its common and complex pathology, especially in the treatment of MPE with lower pH values where TP proved less successful.

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