

Tamoxifen is associated with lower mortality of encapsulating peritoneal sclerosis: results of the Dutch Multicentre EPS Study

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Abstract

Background. Encapsulating peritoneal sclerosis (EPS) is a serious complication of peritoneal dialysis (PD) with an increasing incidence. There is no clear consensus on the treatment of EPS, but anecdotal reports indicate improvement in EPS patients treated with tamoxifen. At present, there is no evidence for the effect of tamoxifen treatment in EPS patients. This study investigates the effect of treatment with tamoxifen on survival in EPS patients.

Methods. This study is a retrospective analysis of survival in EPS patients as part of the Dutch multicentre EPS study in the period January 1996 to July 2007. Sixty-three patients with severe EPS were followed up until August 2008. Demographic, patient and PD-related variables of EPS patients were investigated. Patients treated with tamoxifen were compared to patients not treated with tamoxifen. Survival was analysed with multivariate Cox regression analysis.

Results. Twenty-four patients were treated with tamoxifen, and 39 were not treated with tamoxifen. The clinical and demographic characteristics were similar for the tamoxifen-treated and non-treated groups. The mortality rate was significantly lower in tamoxifen-treated patients compared to EPS patients not treated with tamoxifen (45.8% vs 74.4%, $P = 0.03$). Survival in tamoxifen-treated patients, adjusted for calendar time, age, use of corticosteroids, presence of functioning transplantation, use of parental nutrition and centre influences was longer in comparison to not-treated patients (HR 0.39, $P = 0.056$).

Conclusions. Tamoxifen treatment in EPS patients is associated with lower mortality and shows a trend to an increased multivariate-adjusted survival. This supports additional use of tamoxifen to treat patients with severe EPS.

Keywords: encapsulating peritoneal sclerosis; peritoneal dialysis; survival; tamoxifen

Introduction

Encapsulating peritoneal sclerosis (EPS) is a clinical syndrome characterized by intestinal encapsulation and subsequent obstruction of the intestinal tract by the formation of excessive peritoneal fibrosis tissue [1]. Although EPS can be found in different clinical settings, the condition is most frequently seen in patients treated with peritoneal dialysis (PD).

Although rare, EPS has come to be recognized as a serious complication of PD with a high morbidity and a mortality of approximately 50% [2]. The development of EPS is insidious and probably starts with sterile visceral peritoneal inflammation with neovascularisation, followed by massive deposition of fibrous scar tissue that encases part or all of the bowels. As such, EPS is different from the sclerotic thickening of the peritoneum that appears after many years of peritoneal dialysis, a condition often referred to as simple sclerosis [3]. The inflammatory stage of EPS may be recognized clinically by the appearance of bloody ascites, ultrafiltration failure and signs and symptoms of chronic inflammation. When fibrous tissue progressively encapsulates the bowels, intermittent or definite intestinal obstruction will ensue, leading to severe malnutrition [4,5]. The symptoms of intermittent intestinal obstruction are mild in the beginning of encapsulation and often not appreciated as early signs of EPS.

Due to the slow nature of progression and the aspecific criteria for the EPS diagnosis, there is often a delay in diagnosing the disease. Eventually, the diagnosis is primarily

confirmed by radiological findings or by the macroscopical image of peritoneal encasement. Recently, criteria for abdominal computerized tomography (CT) scanning have been established, which can be of help in diagnosing EPS [6]. Supportive care with either enteral or parenteral nutrition has been shown to be beneficial and should be the mainstay of the treatment when intestinal obstruction with malnutrition is present [7]. Encouraging results from Japan have been reported with surgical enterolysis, releasing the complete small intestine [8]. However, there is little experience with this procedure outside Japan, and it is rarely performed in Western Europe. There is no uniform medical management strategy for EPS, as the efficacy of the intervention is not proven. Usually, patients are treated with intestinal rest and additional treatment, such as immunosuppressive medication [9–11] or tamoxifen [12].

Tamoxifen is a selective oestrogen receptor modulator (SERM) [13], predominantly used for the treatment of breast cancer [14–16]. Tamoxifen also influences the activity of the profibrotic cytokine TGF- β and has been shown to be effective in fibrotic diseases as retroperitoneal fibrosis [17] and Riedels' thyroiditis [18]. The reported effects of tamoxifen in EPS are equivocal and result from a limited number of case reports and small series of patients [12,19,20]. A controlled study investigating the effect of tamoxifen on survival in a larger population is lacking.

Recently, we performed a large Dutch multicentre study to investigate the incidence of EPS in recent years [21], preceded by an initial report indicating a possible increase of EPS [22]. As part of this study, we investigated the survival of EPS patients treated with tamoxifen in comparison with not-treated patients in the period of 1997–2007.

Materials and methods

Design and setting

The design of the study was a retrospective multicentre study. The participating centres were five university hospitals in the Netherlands and three large teaching hospitals. All cases in the participating centres in the study period 1996–2007 were identified by investigating the medical records. The university centres are the primary transplantation centres for their region.

The study protocol was approved by the medical ethics committee of the Erasmus University Medical Centre, Rotterdam.

Classification and diagnosis of EPS

Encapsulating peritoneal sclerosis was defined according the criteria developed by the Ad Hoc Committee of the International Society of Peritoneal Dialysis (ISPD) [23]. It is defined as a clinical syndrome with persistent or recurrent presence of intestinal obstruction with or without the existence of inflammation parameters and the existence of peritoneal thickening, sclerosis, calcifications and encapsulation confirmed by macroscopic inspection or radiological findings.

Using this definition of EPS, the studied population was limited to severe forms of intestinal obstruction that lead to persistent clinical problems, the necessity of surgical intervention, immunosuppressive therapy and/or the necessary use of total parenteral nutrition (TPN).

Participants

Patients with EPS diagnosed in the period 1 January 1996 to July 2007 were included. Medical records of patients with EPS were reviewed in detail by the investigating nephrologist, who was not the primary treating physician. Data were entered into the case report form and database. The date of diagnosis of EPS was retrospectively set at the date at which the

diagnosis fulfilled the definition of EPS and confirmed by two separate nephrologists. All patients underwent abdominal CT scanning.

Outcomes and follow-up

Demographics, patient and PD-related variables were investigated. The duration on PD was calculated by accumulating all separate episodes on PD. Whenever a patient was on another renal replacement therapy for longer than a week, this time was not included in the calculated time on PD. The follow-up on the included patients was extended to August 2008.

Renal replacement therapy was scored at the time of diagnosis of EPS. All episodes of peritonitis were scored. Variables related to kidney transplantation were also investigated. All dates of kidney transplantations were noted. The time after last transplantation until EPS diagnosis was calculated. All immunosuppressive medication was scored as ever used.

To ensure a complete record of medication, all medical records, including electronic prescription software (when used in the hospital) were investigated. Tamoxifen used for the treatment of EPS was scored if the use was longer than 2 weeks. The use of prednisone both intended for treatment of EPS or as part of post-transplant regimen was scored if it was used at the moment of EPS diagnosis or after the diagnosis of EPS was made. The use of parenteral nutrition and azathioprine because of EPS was also scored as ever used.

Statistical methods

Data were entered, and statistical tests were done in SPSS 15.0.1 datamanager (Chicago, USA). Means were compared using unpaired *t*-tests. Proportions were compared with chi-square tests. A two-sided *P*-value of <0.05 was considered to be statistically significant.

Survival was further analysed with Kaplan–Meier and Cox regression analysis. In a multivariate Cox model, we adjusted for the possible confounders age, year of diagnosis, presence of a functioning kidney transplant at time of diagnosis, PD centre, the use of concomitant prednisone and the use of TPN.

Results

Patient characteristics

In the period 1 January 1996 until 1 July 2007, 63 cases of EPS occurred in the participating centres. Within the EPS multicentre study, prevalence was calculated using only the number of patients in the period 1 January 1996 until 1 January 2007. In this period, there were 61 patients diagnosed with EPS, and 2022 patients were on PD in the participating centres. Six EPS patients were excluded from these 61 patients because they had originally started PD in other PD centres than those participating, resulting in a prevalence of 2.7% [21].

For the remaining tests, all 63 EPS patients were used. All 63 patients had objective symptoms of bowel obstruction, underwent abdominal CT scanning and were diagnosed with EPS according the ISPD criteria. Twenty-four patients were treated with tamoxifen, and 39 patients were not treated with tamoxifen.

There were no significant differences between the two groups in ages at start of PD, at EPS diagnosis, at last kidney transplantation or at death. The groups were also comparable concerning follow-up time and the type of renal replacement at the time of the diagnosis (Table 1).

PD and kidney transplantation-related variables

There were no significant differences between the treated and not-treated groups of EPS patients with regards to

Table 1. Patient characteristics

	Total (n=63)	Tamoxifen		P-value
		Yes (n=24)	No (n=39)	
Gender (f/m)	21/42	6/18	15/24	NS
Age				
Age at diagnosis EPS	43.4 ± 14.4	44.7 ± 13.6	42.7 ± 15.1	NS
Age at start PD	34.7 ± 15.4	36.0 ± 14.6	34.3 ± 16.4	NS
Age at death or end of study	45.1 ± 14.1	46.4 ± 13.2	44.3 ± 14.8	NS
Age at last transplantation	36.4 ± 13.4	39.9 ± 15.1	34.0 ± 12.0	NS
Periods				
Time until death after EPS	27.3 ± 20.6	30.8 ± 18.6	25.2 ± 21.7	NS
Follow-up	129.4 ± 60.5	134.8 ± 65.6	126.0 ± 57.7	NS
Renal replacement when EPS				
PD	16	7	9	NS
HD	29	8	21	NS
Functioning graft	18	9	9	NS
End of study				
Deceased	40	11	29	0.03
EPS related death	35	11	24	NS
Alive, functioning graft	9	6	3	0.07
Alive HD	14	7	7	NS
Alive, PD	0	0	0	NS

Data shown as means ± SD. f, female; m, male. Age expressed in years. Time periods expressed in months. Renal replacement therapy expressed in number of patients. Means were compared using unpaired *t*-tests. Proportions were compared with chi-square tests. A two-sided P-value of <0.05 was considered to be statistically significant. NS, not significant.

Table 2. PD and transplantation-related variables in EPS patients

	Total (n = 63)	Tamoxifen		P-value
		Yes (n = 24)	No (n = 39)	
PD				
Time on PD	77.4 ± 38.1	69.9 ± 35.1	82.0 ± 39.5	NS
Episodes of peritonitis	4.1 ± 3.8	3.9 ± 3.6	4.2 ± 3.9	NS
Transplantation				
Number of patients	47	19	28	NS
Number of transplantations	1.6 ± 0.9	1.4 ± 0.9	1.7 ± 0.9	NS

Time periods and episodes of peritonitis shown as means ± SD. PD, peritoneal dialysis. Time periods expressed in months. Number of transplantations expressed as means ± SD per transplanted patient. Means were compared using unpaired *t*-tests. Proportions were compared with chi-square tests. A two-sided P-value of <0.05 was considered to be statistically significant. NS, not significant.

the cumulative period on PD, the episodes of peritonitis, the number of transplanted patients and the number of transplantations per transplanted patient. Overall, 47 transplanted patients developed EPS after the last kidney transplantation with a mean of 50.8 ± 69.8 months after the last kidney transplantation. Mean age at the last transplantation was 36.4 ± 13.4 years. Twenty-one patients with a kidney transplant (44.7% of the total 47 transplanted patients) developed EPS within 2 years after the last kidney transplantation (Table 2).

Among the 47 patients with EPS after transplantation, 18 patients had a functioning kidney transplant at the time of EPS diagnosis (Table 1). None of the patients was transplanted because of EPS symptoms.

EPS treatment

There were no differences between the groups of EPS patients with respect to the treatment with TPN or prednis-

one. The total number of patients using prednisone (patients using prednisone for the treatment of EPS or as part of post-transplant regimen combined) was also not different between the groups. In each group, one patient treated was also treated with azathioprine (Table 3). Treatment with tamoxifen was started by the treating physician. Dosages of tamoxifen varied in time from 10 mg once a day to 20 mg twice a day. All patients in the treatment group were treated with tamoxifen for at least 4 weeks. There was no enterolysis performed in any of the patients.

Outcome

The overall mortality rate was lower in tamoxifen-treated patients compared to the patients not treated with tamoxifen, respectively, 11 out of 24 and 29 out of 39 patients (45.8% vs 74.4%), $P = 0.03$. Estimated survival analysed with Kaplan–Meier showed better survival in the group treated with tamoxifen ($P = 0.07$, Figure 1). Univariate

Table 3. Treatment of EPS

Treatment for EPS	Tamoxifen		P-value
	Yes (n=24)	No (n=39)	
Parenteral nutrition	14	21	NS
Prednisone	11	9	NS
Azathioprine	1	1	NS
Prednisone total use	12	14	NS

Data shown as number of patients. Prednisone total use means patients treated with prednisone because of EPS and because of renal transplant after the moment of EPS diagnosis. Proportions were compared with chi-square tests. A two-sided P-value of <0.05 was considered to be statistically significant. NS, not significant.

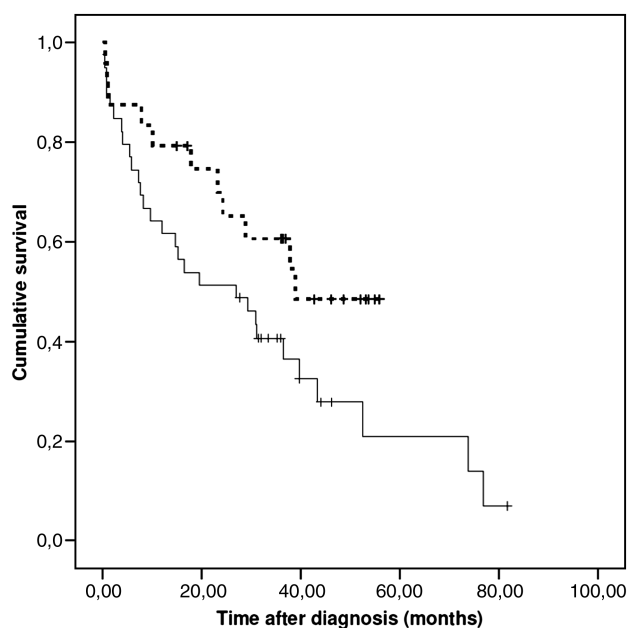


Fig. 1. Survival of EPS patients with and without treatment with tamoxifen. Kaplan-Meier analysis showing survival of 24 patients treated with tamoxifen (dashed line) and 39 patients without tamoxifen (solid line). Time after diagnosis means time in months after EPS diagnosis. + Means censored in analysis. P-value was 0.077.

Cox regression analysis confirmed this trend with a hazard risk (HR) of 0.54 ($P = 0.08$). Multivariate Cox regression analysis with adjustment for age, year of diagnosis, presence of a functioning kidney transplant at time of diagnosis, PD centre, use of concomitant prednisone and the use of TPN also showed a trend to an improved survival in the tamoxifen-treated group, although the level of statistical significance did not reach the predefined limit of <0.05 (HR 0.39, $P = 0.056$).

Discussion

The present study shows that mortality rate is lower in tamoxifen-treated EPS patients compared to EPS patients not treated with tamoxifen with both groups having comparable demographic and clinical characteristics. More im-

portantly, treatment of EPS patients with tamoxifen was associated with a trend to an improved survival, independent of other possible beneficial treatment options. In accordance with previous studies, the results identify EPS as a life-threatening condition with a very high mortality.

At present, there are no randomized controlled trials that have shown the efficacy of any given drug for EPS. Because there is a presumed inflammatory response in the early development of EPS, corticosteroids are often given. Other immune suppressive agents like azathioprine, mycophenolate mofetil or sirolimus have been given on a smaller scale. The beneficial effects of this immune suppressive therapy are predominantly anecdotal [10,24–29], and undoubtedly this is a biased view because negative results are not likely to be reported.

In addition, a beneficial effect of immune suppressive medication appears to be in contrast with our finding that EPS is more likely to develop in the first year after renal transplantation, when patients are already immunosuppressed [22,30]. In this study, we could not identify a beneficial effect of prednisone on survival of EPS patients. Therefore, the effect of immunosuppressive medication for the treatment of EPS remains to be proven.

Similar to immune suppressive medication, various anecdotal experiences and small case series have been reported on the effects of tamoxifen in EPS patients [12,19,20,31–40] and are summarized in Table 4. All reports show improvement of the intestinal function and a decrease of inflammatory markers, except for a recently published large case series from England [19]. In this latter study, survival time in various treatment groups, including in 31 patients treated with tamoxifen, was not different compared to patients not given any drug treatment. This apparent discrepancy to our results may result from inclusion of less severe cases of EPS in the English study. For instance, only 33% of the English patients had a clinical diagnosis of bowel obstruction, while all patients in the present study had objective signs of severe bowel obstruction, necessitating parenteral nutrition in 35 of the 63 EPS patients.

In addition, the comparison appears inappropriate due to a possible difference in aetiology of EPS. In the UK study, only 14 out of 111 patients developed EPS with a functioning renal transplant compared to 18 out of 63 in our study (out of the total of 47 transplanted patients). The latter reflects our previous reported high incidence of EPS shortly after renal transplantation [22]. From the other reports on the effect of tamoxifen, only Moustafellos *et al.* report patients with post-transplant EPS [34]. A different response of post-transplant EPS to tamoxifen is not implausible, considering that in this condition the peritoneal inflammatory-fibrotic processes may be accelerated [30].

Our study was not randomized. Although we did take into account all available possible confounders by including them into a multivariate analysis, it is possible that the results are influenced by ‘confounding by indication’.

Recently, EPS has received increasing attention, and subsequently there might be an improved strategy or increased use of tamoxifen in time. It is unlikely that this acts as a confounder because the year of diagnosis was included in the analyses. A limitation of the study is the fact that treated patients were retrospectively compared to patients

Table 4. Reports on tamoxifen in EPS

Study	Report	N	Dose of tamoxifen	Steroids	Outcome
Turner <i>et al.</i> [40]	Case	1	10 mg b.i.d.	No	Improvement
Allaria <i>et al.</i> [31]	Case	1	10 mg q.d.	No	Improvement (3 months FU)
Pollock <i>et al.</i> [32]	Case	1	10 mg q.d.	Yes	Improvement
Del Peso <i>et al.</i> [39]	Series	9	20 mg b.i.d.	NR	Survival benefit
Evrenkaya <i>et al.</i> [33]	Case	1	10 mg q.d.	Yes	Improvement (2 months FU)
Korzets <i>et al.</i> [38]	Series	2	20 q.d. to 40 mg b.i.d.	Yes	Deceased
Moustafellos <i>et al.</i> [34]	Series	2	20 mg b.i.d.	Yes	Improvement (3–4 months FU)
Dogan <i>et al.</i> [36]	Case	1	10 mg q.d.	Yes	Resolved
Mesquita <i>et al.</i> [37]	Case	1	20 mg b.i.d.	Yes	Improvement
Eltoum <i>et al.</i> [12]	Series	4	20 mg b.i.d.	No	Resolved
Thirunavukarsara <i>et al.</i> [35]	Series	2	20 mg q.d.	No	Improvement (6 months FU)
Gupta <i>et al.</i> [20]	Case	1	20 mg b.i.d.	No	Improvement
Balasubramaniam <i>et al.</i> [19]	Series	31	NR	Yes (12)	No survival benefit
Korte <i>et al.</i> (present study)	Series controlled	24	10 mg q.d. to 20 mg b.i.d.	Yes (12)	Survival benefit (P = 0.056)

N means number of EPS patients treated with tamoxifen; b.i.d., twice daily; q.d., once daily; NR, not reported and FU, follow-up. The additional use of steroids is mentioned with number of patients when available. In the report of Eltoum *et al.*, all four patients had restored intestinal function.

who were not treated. Perhaps, physicians are more likely to prescribe or retain certain drugs in more severe cases. Another possible confounder is the fact that non-tamoxifen-treated patients tend to have more haemodialysis (HD) at the time of EPS diagnosis. This could imply that patients on HD are sicker and are less likely to receive tamoxifen. We minimized these possibilities by using strict definitions of EPS, including only severe cases with intestinal obstruction.

Due to the nature of the study, we were not able to report the median dosage or cumulative exposure to tamoxifen. In the present study, we could not include the influence of enterolysis, since such a procedure was not applied in our study population.

During the development of peritoneal sclerosis, in which an inflammatory state develops into a fibrotic stage, neoangiogenesis and the transition of mesothelial cells with epithelial phenotype to mesenchymal type (EMT) with fibroblast-like characteristics are essential [41]. In this process, TGF- β and vascular growth factors have a pivotal role. TGF- β is regarded to be a central mediator of EMT [42]. Overexpression of TGF- β in an animal model with chronic high glucose PD fluid exposure resulted in peritoneal fibrosis and neoangiogenesis [43]. Myofibroblasts originating from the epithelial phenotype mesothelial cell produce vascular growth factors leading to neoangiogenesis and vasculopathy. In long-term PD, these vascular changes with upregulation of vascular growth factors were shown [44]. Blockade of these factors and inhibition of angiogenesis showed reduced angiogenesis and slowed the peritoneal fibrosis, confirming the important role of vascular growth factors in peritoneal fibrosis and possibly EPS [45–47].

The antifibrotic effects of tamoxifen seem to be related to the influence of TGF- β and inhibition of angiogenesis. In other diseases with excessive collagen deposition and involvement of TGF- β , like Dupuytren's, tamoxifen was able to downregulate the TGF- β production [48]. In oncology, levels of vascular endothelial growth factor (VEGF) are associated with the extent of angiogenesis and have prognostic value. Tamoxifen decreased extracellular VEGF

level in solid tumours [49] and attenuated VEGF-mediated angiogenesis [50]. Extrapolating these findings, tamoxifen might ameliorate the process of peritoneal fibrosis by downregulating TGF- β and decrease VEGF levels, thereby inhibiting angiogenesis.

Patients with EPS development are historically treated with transfer to HD, nutritional support or more recently with enterolysis. Given the clear pathophysiological rationale for using tamoxifen in EPS patients combined with the encouraging results from this study, this may be a promising additional treatment option for a condition with a high mortality. To further establish our findings, a randomized controlled trial has to be performed. Given the low frequency of EPS, such a study should be performed in a large research collaboration [51].

When tamoxifen is considered as part of the treatment of EPS, potential adverse effects of the drug must be taken into account. Most reported adverse effects are thromboembolism, endometrial carcinoma or strokes [14]. Only Eltoum *et al.* reported on the adverse events [12]. They observed three episodes of thromboembolic disease in four EPS patients. Our retrospective design of the study did not allow for an adequate evaluation of possible tamoxifen-related adverse events. Due to the morbidity and the limited life expectancy of EPS patients, the benefits of tamoxifen probably outweigh the potential risks.

In conclusion, this study shows that tamoxifen treatment is associated with a lower mortality and shows a trend to a higher multivariate-adjusted survival of EPS patients. In addition to supportive therapy, tamoxifen may therefore improve the prospect of this severe condition.

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Osmotic nephrosis due to the use of anti-adhesive membrane intraperitoneally

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Abstract

Background. A common strategy for the prevention of intra-abdominal adhesions post-operatively has been the application of adhesion barriers into the peritoneal cavity. Side effects of these barriers are infection, abscesses and inadequate wound healing. There is no information about such a side effect of these materials on renal function. The aim of this study was to evaluate the effect of two different, commercially available polysaccharide-based anti-adhesive materials on renal function.

Methods. In 24 adult Wistar rats, an abdominal midline incision was performed, and an anti-adhesion membrane was placed in the peritoneal cavity so as to cover its whole surface. Four rats were used as the control group. In 12 rats, a membrane of macromolecular polysaccharides, weighing 40 mg/cm², was placed intra-abdominally and in 8 rats, a hyaluronic acid-hydroacidmethylcellulose membrane weighing 0.4 mg/cm² was placed. At 24 or 70 h, the rats were sacrificed, and we evaluated changes in serum creatinine, urea, uric acid, K and Na, and histologic examination of the kidney was performed.

Results. The use of the thicker macromolecular membrane was associated with a rise in serum creatinine and urea levels, vacuolization of all the tubular epithelial cells and mild interstitial infiltration. Rats in which the hyaluronic

acid-hydroacidmethylcellulose membrane was used did not show any creatinine elevation, and they presented milder histologic lesions.

Conclusion. Polysaccharide and cellulose anti-adhesive membrane cause renal damage with tubular cell vacuolization. The severity of kidney damage is relative to the quantity of the membrane material used.

Keywords: acute renal failure; anti-adhesive barriers; macromolecular polysaccharides; osmotic nephrosis

Introduction

Major intra-abdominal surgery and peritoneum inflammation are a common cause of adhesions in the peritoneal cavity. Post-operative adhesions often elicit symptoms such as abdominal pain and have been associated with bowel obstruction and female infertility [1]. A practical preventive technique used to minimize post-operative adhesions is the placement of adhesion-reducing agents in the abdomen intra-operatively.

A variety of different materials have been used as adhesion-reducing agents in experimental as well as in clinical trials, including substances with anti-inflammatory, fi-