Trakia Journal of Sciences, Vol. 9, No 1, pp 17-23, 2011

Available online at:
http://www.uni-sz.bg

ISSN 1313-7050 (print)
ISSN 1313-3551 (online)

Original Contribution

CHRONIC PLEURAL CHANGES AFTER INTRAPLEURAL INSTILLATION OF IODPOVIDONE – EXPERIMENTAL STUDY IN RABBITS

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ABSTRACT

Pleurodesis, from the Greek *pleura* and *desis* (binding together), is intended to achieve a symphysis between parietal and visceral pleura, in order to prevent accumulation of either air (pneumothrax) or fluid (pleural effusion) in the pleural space. The search for the ideal agent for pleurodesis continues. The aim of this research was to assess the chronic gross and microscopic pleural findings, after intrapleural administration of *iodpovidone* as a sclerosing agent. 12 New Zealand White rabbits were used for the study. After instillation of 2 ml 10% iodpovidone into the right pleural cavity, the animals were sacrificed in groups of three on day 5, 7, 10, 14. Gross pathology and histology analysis were performed. It was established, that jodpovidone has caused pleural inflammation whit mononuclear cells infiltration and formation of new blood vessels on day 5. It was also established expressive proliferation of fibroblasts within visceral pleura and collagen production. The final result was fibrotic transformation of the visceral pleura, which was established on day 14. As a result of pleural fibrotic transformation, complete obliteration of the pleural space occurred, which means effective pleurodesis. The study had shown that intrapleural instillation of iodpovidone has caused effective pleurodesis until the period of 14 days. The safeness of iodpovidone as an agent for chemical pleurodesis has also been proven in the study.

Key words: iodpovidone, pleural inflammation, pleurodesis,

INTRODUCTION

Pleurodesis is frequently employed worldwide in the management of malignant pleural effusion and control of recurrent pneumothorax. Pleurodesis (*pleura* and *desis* = binding together), is intended to achieve a symphysis between parietal and visceral pleura, in order to prevent accumulation of either air (pneumothrax) or fluid (pleural effusion) in the pleural space (1, 2). The methods of pleurodesis include surgical abrasion with a dry gauze sponge through thoracotomy or video-assisted thoracoscopic surgery (VATS), or intrapleural instillation of a sclerosant agent through tube thoracostomy or through VATS (2, 3).

The ideal agent for chemical pleurodesis should be easily administrated, inexpensive and widely available. It should induce minimum morbidity and be 100% effective [2, 4]. Many different agents have been used to achieve a pleurodesis, but none of them meet all of these criteria. Searching an "ideal" agent for pleurodesis demands precisely knowledge about mechanism of pleurodesis, causing by it.

Iodpovidone is one of the agents used for chemical pleurodesis. It is available and inexpensive iodine-based topical antiseptic (5, 6, 7, 8, 9). In our previously experimental survey we have already determined the acute pleural changes caused by iodpovidone. The present study represents continuation of our work in studying the exact mechanism of pleurodesis, caused by iodpovidone. The objective of this experimental study was to assess the chronic pleural findings after intrapleural instillation of iodpovidone.

MATERIAL AND METHODS

Twelve New Zealand male rabbits weighting 2, 5-3, 5 kg were used in this study.

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Experimental procedure:
The animals were lightly anesthetized with 35 mg/kg ketamine hydrochloride, injected intramuscularly. The right hemithorax was prepared for aseptic surgery by shaving and then cleaning it with t-ra Jodi and alcohol. A 3-cm skin incision was made midway between the spine and the scapular tip. The muscles in the sixth or seventh intercostals space were bluntly dissected to allow exposition of the parietal pleura. A specially prepared multi-perforated catheter (from the 22-G angiocatheter) was introduced into the pleural space. 2 ml 10% iodpovidone were injected trough the catheter into the right pleural cavity of all rabbits. In sequence, the catheter was removed and the muscles and skin were sutured.

The animals, in group of three, were sacrificed after 5, 7, 10, 14 days of the intrapleural instillation of iodpovidone with lethal dose of 50 mg/kg of thiopental injected into the marginal ear vein.

Gross pathology:
In the supine position, the sternum and the median portions of the ribs were removed so the two hemithoraces could be evaluated macroscopically. The left hemithorax served as a control. The pleural changes were documented by digital photography. The degree of pleurodesis observed grossly was graded according to the following scheme:

0. normal pleural space and lung;
1. fibrin deposition onto pleural surfaces;
2. few scattered adhesions and fibrin strands between pleural surfaces ;
3. generalized adhesions and fibrin strands between pleural surfaces;
4. completely obliteration of the pleural space.

Tissue specimen preparation:
At the time of the gross evaluation of the pleural space, samples of the visceral pleura and lung from the right hemithorax were obtained. The specimens have been placed in 10% formalin solution for two days and fixed in paraffin. Histological sections were prepared routinely and stained with hematoxylin and eosin. The microscopic slides were evaluated by light field microscopy (x 100,200,400) for the presence of inflammation and fibrosis.

Animal care:
We adhered to the "Guide to the Care and Use of Experimental Animals" in the course of the whole study. (10)

Results:
Gross pathology:
Sero-fibrinous effusions were established in the right pleural space on the fifth day of intrapleural instillation of iodpovidone. There was fibrin deposition onto the pleural surfaces and fibrin strands and adhesions between them **(fig. 1)**. The degree of pleurodesis was established as 2.

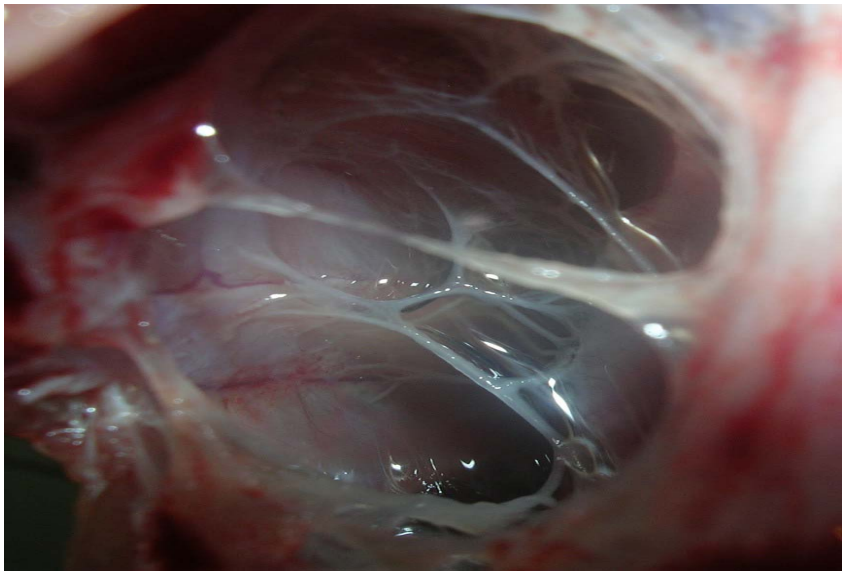

Figure 1. Digital photography on 5 day. The sternum and the median portions of the ribs are removed. Fibrin strands between pleural surfaces.

On the day 7 there were more fibrin strands and adhesions between pleural surfaces, with fibrin deposition onto them **(fig. 2)**. The degree of pleurodesis was established as 2,5.

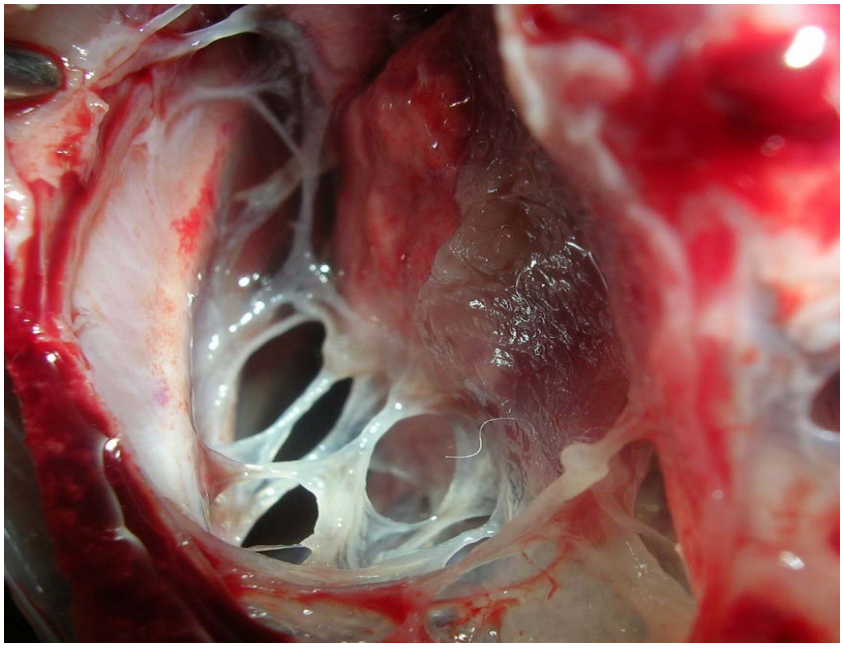

Figure 2. Digital photography on 7 day. More than 5 day fibrin strands between pleural surfaces.

There were generalized fibrinous strands and adhesions between pleural surfaces on the day 10^{th}. Grossly, thickened visceral pleura with fibrin deposition onto it was established **(fig. 3)**. The score for pleurodesis was 3, 5.

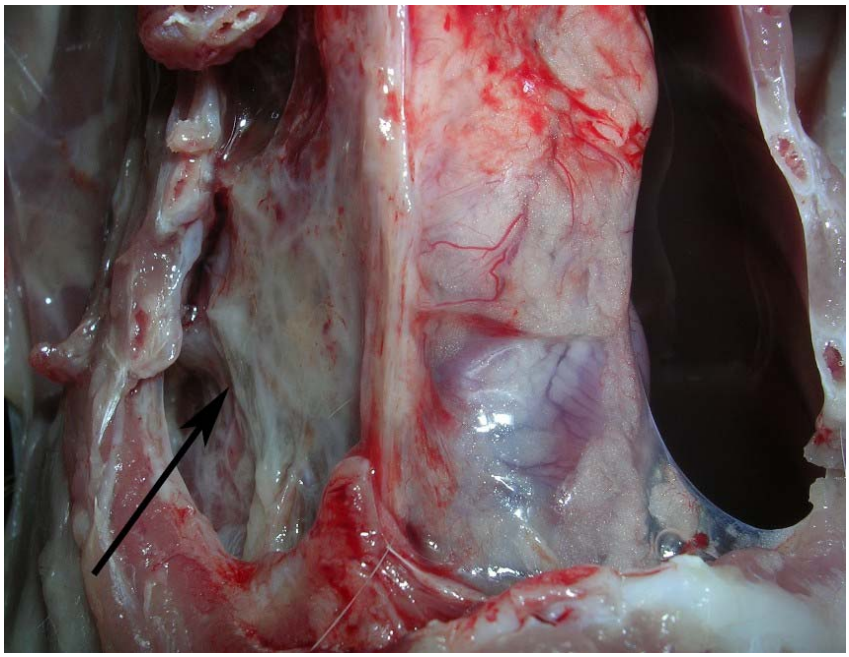

Figure 3. Digital photography on 10 day. The arrow points fibrin deposition onto visceral pleura.

Complete obliteration of the right pleural space was determined on the day 14^{th} after intrapleural instillation of iodpovidone. Macroscopically, fibrotic transformation of the thickened visceral pleura was established **(fig. 4).** The score for pleurodesis for the animals was 4.

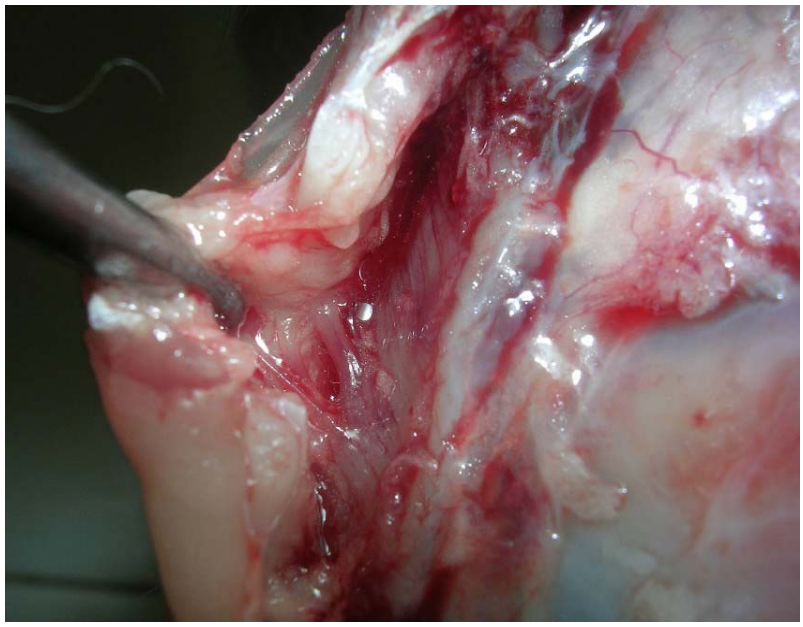

Figure 4. Digital photography on 14 day. There is completely obliteration of the pleural space as a result of fibrous pleural adhesions (effective pleurodesis).

Through out the whole period of the experimental study – 14 days, the left pleural cavity and lung, which were served as a control, weren't changed.

Histologyc analysis:

Specimens, obtained on the 5th day after iodpovidone instillation demonstrated thickened visceral pleura. The inflammatory infiltrates within the visceral pleura were predominantly mononuclear – macrophages and monocytes **(fig. 5)**. There were polimorphonuclear cells among mononuclear infiltration. The same inflammatory infiltrates were established in the subpleural lung parenchyma. Fibroblasts were visibled within the thickened visceral pleura. New blood vessels formation within the pleura has begun even on the 5th day after intrapleural instillation of iodpovidone.

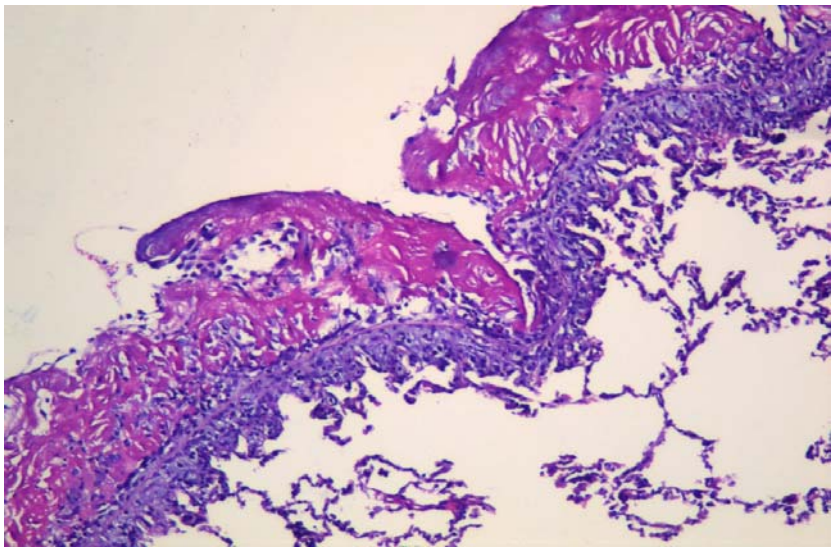

Figure 5. Photomicrograph on day 5 (x 100). Note the mononuclear cells infiltration within the thickened visceral pleura and supleural lung tissue. There is a fibrinuos peel onto the visceral pleura.

On the day 7th there was massive mononuclear infiltrates within the thickened pleura and subpleural lung parenchyma **(fig. 6)**. Lymphocites, were also established in the inflammatory infiltrates. Only a few polimorphonuclear cells were visibled in the inflammatory infiltrates. Many fibroblasts and new blood vessels were established into the thickened visceral pleura.

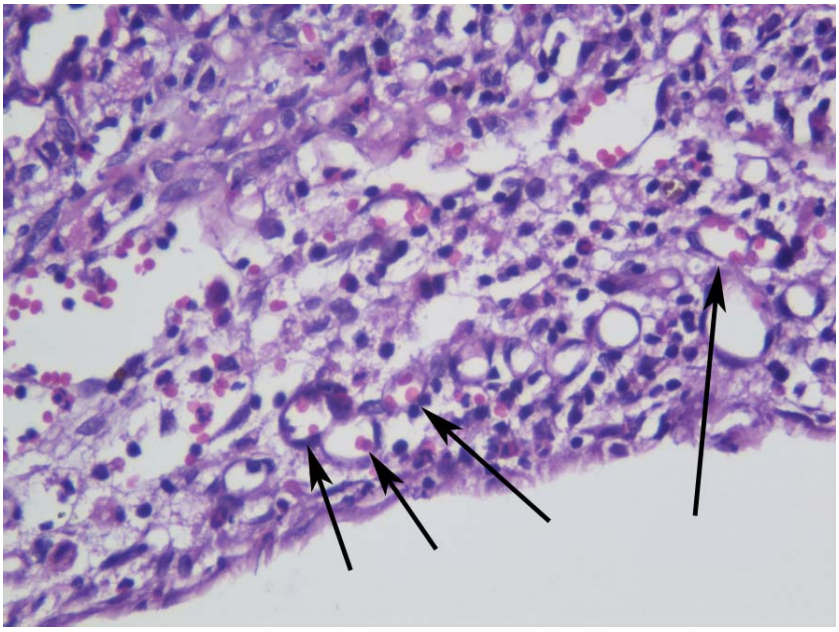

Figure 6. Photomicrograph on day 7 (x400). Note the expressive mononuclear infiltrates within the thickened visceral pleura. The arrows point to the new blood vessels.

The number of fibroblasts within the visceral pleura was increased on day 10th after intrapleural iodpovidone instillation.. Collagen fibers were apparent in the visceral pleura **(fig. 7)**. The blood vessels of thickened pleura decreased in size and number. There was significant resolution of cells infiltrates in the pleura and subpleural lung parenchyma.

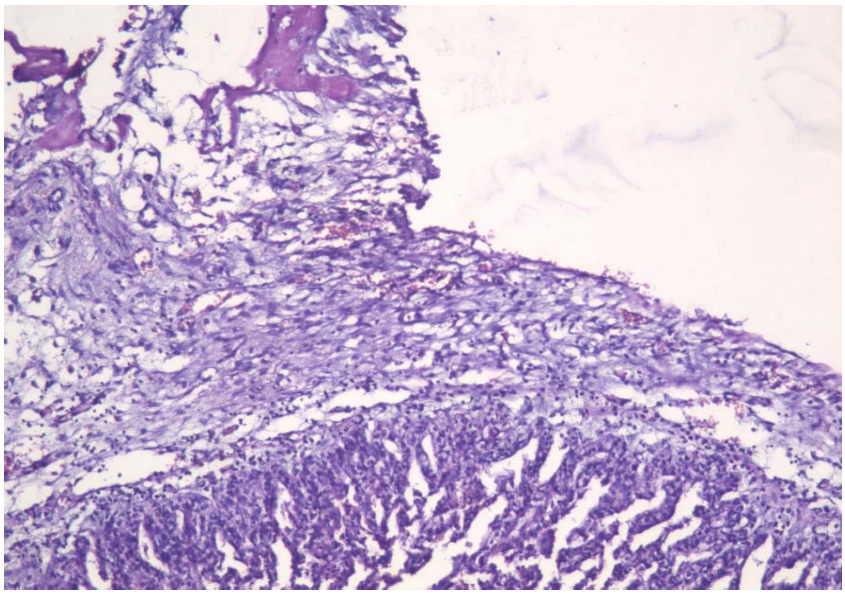

Figure 7. Photomicrograph on day 10 (x100). Note the fibroblasts and collagen fibers within the thickened visceral pleura. The blood vessels are decreased in size and number.

The greatest pleural thickness was observed on day 14th. The thickened visceral pleura mainly consisted of collagen fibers with many fibroblasts between them **(fig. 8)**. The blood vessels in the thickened pleura were significantly decreased in size and number.

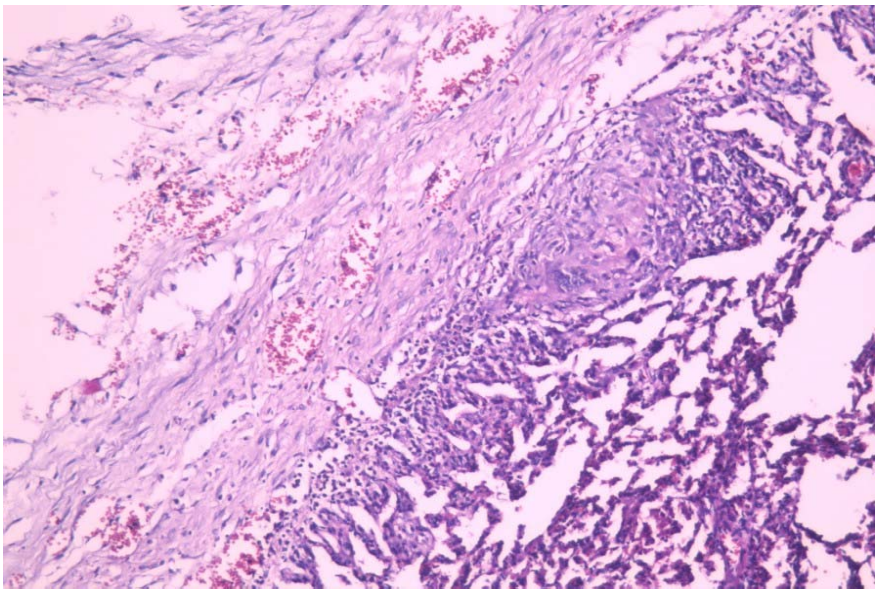

Figure 8. Photomicrograph on day 14 (x100). There is fibrous transformation of the visceral pleura. Note the collagen fibers with many fibroblasts between them.

Microscopically, the fibrin strands between pleural surfaces were established on day 5, 7 and 10. The fibrin strands have had the same inflammatory cell infiltration like the thickened visceral pleura. On day 5 and day 7 the strands were infiltrated predominantly with mononuclear cells. On day 10 it was established organization of the strands as a result of fibroblast proliferation and collagen production.

DISCUSSION

Several clinical studies have reported iodpovidone as an effective agent for pleurodesis (5, 6, 7, 8, 9). Even though, we founded out that there are not publications on mechanism of pleurodesis caused by iodpovidone. That's why we decided to study the mechanism of jodpovidone-pleurodesis with the goal of using it as a pleural sclerosant in our clinical practice. In our first experimental study we established that intrapleural injection of iodpovidone has caused acute pleural inflammatory reaction. We demonstrated that mesothelial cells injury and dilatation of subpleural vessels is the trigger of this pleural inflammation. It had been determined that the 4th day represented the border time between acute and chronic pleural changes, caused by intrapleural injection of iodpovidone. That's why as the next step – studying the chronic pleural changes, in the present study, we have been investigated pleural changes in animals after 4 day of intrapleural injection of iodpovidone.

Several grossly findings have proved progression of pleural inflammation, caused by iodpovidone. At first, it was established enlargement in size and number of fibrin strands between pleural surfaces. Pleural exudate became thick, with progressive fibrin deposition on all pleural surfaces. Second, the thickened visceral pleura, transformed in fibrous peel and complete obliteration of the pleural space on day 14, are evidences of fibrous transformation during the organizing phase (chronic stage) of pleural inflammation.

In the present study, we have demonstrated microscopically, as well as grossly, progression of pleural inflammation, caused by jodpovidone. First of all, pleural infiltrates, consisted of mononuclear cells and lymphocytes are signs of progression of pleural inflammation into its chronic stage. Second, the increase in both size and number of blood vessels within the thickened visceral pleura is a sing of activated angiogenesis during pleural inflammation.

It is proven that cells in inflammatory infiltrates produce growth factors (cytokines) [11]. Growth factors stimulate influx of fibroblasts into the inflammatory visceral pleura from subpleural lung parenchyma. Growth factors also activate fibroblast proliferation into the pleura. Growth factors also activate fibroblast collagen synthesis. As a result of fibroblast proliferation and collagen synthesis, fibrous pleural transformation has occurs (12, 13, 14, 15). The structure of pleura has changed. We have demonstrated this

pleural transformation. We have established that on the day 14 pleura was represented as fibrous peel with significantly resolution of cells infiltrates and decrease of blood vessels in size and number on it. As a result of fibrous transformation, fibrous adhesions between pleural surfaces have occurred, with completely obliteration of the pleural space. This is a sing of effective pleurodesis, caused by intrapleural instillation of iodpovidone.

Our results have demonstrated that iodpovidone, injected in the pleural cavity of the animals had caused pleural inflammation, with progression through acute to chronic stage in a 14 days period. With pathological changes in this study – pleural inflammatory cells infiltration, angiogenesis, fibroblast proliferation and collagen production, we have confirmed the hypothesis that mechanism of pleurodesis closely resembles the pathogenesis of would healing (1, 16, 17).

With this study, we have demonstrated that iodpovidone did not caused significant changes of the lung parenchyma within the progression of pleural inflammation. There were only reactive inflammatory infiltrates on the subpleural lung tissue. The cell structure of infiltrates was the same as those on the visceral pleura. We have demonstrated almost complete resolution of subpleural infiltrates on the 14th day. That fact, as well as unchanged left pleural cavity of the animals is the evidence of safetyness of iodpovidone as an agent for chemical pleurodesis.

CONCLUSION

Intrapleural instillation of iodpovidone has caused effective pleurodesis for period of 14 days by the mechanism of aseptic pleural inflammation.

This experimental study has proven the safety usefulness of iodpovidone as an agent for chemical pleurodesis.

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