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Safety and Systemic Consequences of Pleurodesis with Three Different Doses of Silver Nitrate in Patients with Malignant Pleural Effusion

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Key Words
Clinical trials · Malignant pleural effusion · Pleurodesis · Pleurodesis agent · Silver nitrate

Abstract
Background: Silver nitrate (SN) is an alternative to talc pleurodesis in patients with malignant pleural effusion (MPE). Nevertheless, SN complications have not been thoroughly investigated so far. ***Objective:*** To evaluate frequent adverse events (AE) of SN treatment at three different doses for pleurodesis in patients with MPE. The secondary objective was to evaluate systemic inflammation, efficacy and quality of life in these patients. ***Methods:*** A double-blind, randomized, clinical trial was conducted in patients with recurrent MPE at a tertiary university hospital. The study patients underwent pleural catheter insertion and were randomly assigned to one of the three pleurodesis groups treated with 30 ml 0.3%, 30 ml 0.5% or 60 ml 0.3% SN. Patients were discharged 3 days after the procedure, and returned to follow-up visits on days 10 and 30. During follow-up, AE, inflammatory markers, quality of life and CT scans were systematically assessed and documented. ***Results:*** Sixty patients (11 males and 49 females, median age 62.13 years) were included. Overall, 199 AE were observed, including 23 serious AE. Grade 1/2 metabolic AE, such as increases in creatinine and liver enzymes, were the most frequent. Grade 3/4 hypoxia was observed in 13 patients. Four patients died, 3 due to disease progression and in 1 patient death was possibly related to pleurodesis. C-reactive protein levels increased in a dose-dependent manner and peaked 48 h after pleurodesis. No significant difference was observed among groups regarding quality of life or clinical/radiological recurrence. ***Conclusion:*** Hypoxia was the most significant AE following SN pleurodesis; mild metabolic events were very common. SN instillation causes substantial dose-dependent systemic inflammatory responses.

Introduction

Pleurodesis is one of the best options for symptom control in patients with malignant pleural effusion (MPE) [1]. Many sclerosing agents have been studied so far, e.g. bleomycin, talc, silver nitrate (SN) and iodopovidone [1–10]. Currently, the preferred agent is talc due to its effectiveness (success rates of almost 90%), low costs and easy availability [1–5]. Nevertheless, there are concerns regarding the safety of talc, since severe side effects have been reported, e.g. pneumonitis, respiratory failure and even death, following talc pleurodesis [2, 11–14]. These complications have been associated with the size of the talc particles; however, in a large cohort study in patients

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with MPE [5], the use of large-particle talc was associated with only a few respiratory complications and there was no case of adult respiratory distress syndrome.

Unfortunately, large-particle talc is not widely available, and in many countries clinicians resort to nongraded talc or other options. SN is an interesting alternative which is not only cheap and widely available, SN has also shown similar effectiveness compared to talc both in animal and human studies [8, 15–18]. With regard to adverse events (AE), in a small cohort study, 19% of patients who underwent SN pleurodesis had at least one AE [9]. The optimal SN dose and concentration has not been determined yet, and a study in rabbits demonstrated that instillation of 0.3% SN was as effective as the standard dose [19].

Although some studies have addressed the efficacy of SN pleurodesis and even tested the efficacy of different doses, its safety, systemic responses and the most effective dose remain subject to controversy. Therefore, the objective of this study was to evaluate frequent adverse events (>5%) of SN pleurodesis in patients with MPE. The secondary objective was to evaluate systemic inflammation, efficacy and quality of life in these patients and correlate all outcomes with the SN dose.

Patients and Methods

This study was a three-arm, double-blind, randomized, clinical trial conducted from August 2009 until June 2011 in a tertiary teaching hospital in São Paulo, Brazil. All patients were enrolled in our outpatient clinic and inclusion criteria were recurrent and symptomatic MPE (confirmed by cytological analysis and/or pleural biopsy), previous chest radiography showing full lung expansion (>90%) after chest drainage according to two different raters, a Karnofsky performance status >40 and written informed consent. Exclusion criteria were trapped lung after pleural catheter insertion, presence of hemorrhagic diathesis (prothrombin time <50% and platelet count <80,000/mm^3), active pleural or systemic infection, neoplastic infiltration of the skin at the site of pleural catheter insertion, age <18 years, presence of previous ipsilateral pleural interventions (with the exception of thoracentesis and pleural needle biopsies), inability to understand quality-of-life questionnaires and a contralateral pleurodesis <30 days before study entry. Patients should not have received chemotherapy 15 days before pleurodesis, and chemotherapy was postponed for more than 15 days after pleurodesis.

This study was registered both under our institution's Ethics Committee (CAPPesq HCFMUSP 1041/09) and ClinicalTrials.org (NCT01125124).

Groups, Randomization and Blinding

Two different concentrations of SN were used in this study: 0.3% SN (a lower SN concentration which showed the same efficacy as the standard one in an experimental study [19]) and 0.5% SN (standard concentration); 300 mg (0.3% SN) or 500 mg (0.5% SN) of SN (Merck, Darmstadt, Germany) were dissolved in 100 ml of distilled water to form a homogeneous solution which was passed through a 0.22-μm porosity filter to ensure sterility. The time interval between preparation and pleural instillation did not exceed 6 h.

Groups were divided according to the concentration and volume of SN instilled in the pleural cavity. Group 1 received 30 ml of the 0.3% solution (total: 90 mg) of SN. Group 2 received 30 ml of the 0.5% solution (total: 150 mg) of SN. Group 3 received 60 ml of the 0.3% solution (total: 180 mg) of SN.

Patients were assigned to one of the three groups by block randomization, and only pharmacy employees and clinicians who instilled the sclerosing agent were aware of the group allocation. Clinicians who instilled SN were not involved in the patients' follow-up. Patients, investigators that followed patients and rated their complications, and those who performed statistical analyses were blinded to the group allocation.

Procedure

After signing a consent form, patients were admitted to our ward where they remained for 5 days. On the 1st day, patients were asked to answer the Portuguese language-validated [20] World Health Organization Quality of Life bref (WHOQoL-bref) questionnaire. They were also asked to answer the Visual Analogue Scale (VAS) for chest pain and the UK Medical Research Council Dyspnea Scale (MRC). Hematologic, inflammatory, renal and hepatic blood parameters were also assessed. Patients then underwent chest drainage with a 14-Fr pigtail catheter (C-UPTP-1400-WAYNE; Cook Medical, Bloomington, Ind., USA) under ultrasound guidance. Board-certified thoracic surgeons performed all procedures.

On the 2nd day, patients were asked to answer the VAS and MRC and blood samples were again collected and analyzed. They were then randomized to one of the three groups previously described and underwent bedside pleurodesis. Depending on the group allocation, 30 or 60 ml of the solution were instilled through a catheter, which was closed for 1 h following instillation and subsequently reopened. The analgesic method of choice was 1 g of dipyrone upon patient request (maximally 4 g daily). In case of severe and dipyrone-refractory pain, patients received 100 mg of tramadol.

On days 3–5, patients were asked to answer the VAS and MRC scales, and blood samples were collected and analyzed. On day 5, patients also underwent a chest CT, had their chest tube removed and were discharged.

Within 5 and 25 days of discharge, patients returned to our outpatient clinic. They were asked to answer the VAS and MRC and blood samples were again collected and assessed. CT was repeated 30 days after pleurodesis. Patients who did not present at the scheduled visits were contacted by telephone.

Definitions and Outcome Assessment

We adopted the FDA definition of AE: 'Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related' [21]. The primary outcome was safety, a binary variable (yes/no) based on the occurrence of 'serious' or severe AE during follow-up. We defined AE of grade 3 or higher as serious, according to the National Cancer Institute Common Terminology Criteria for Adverse Events

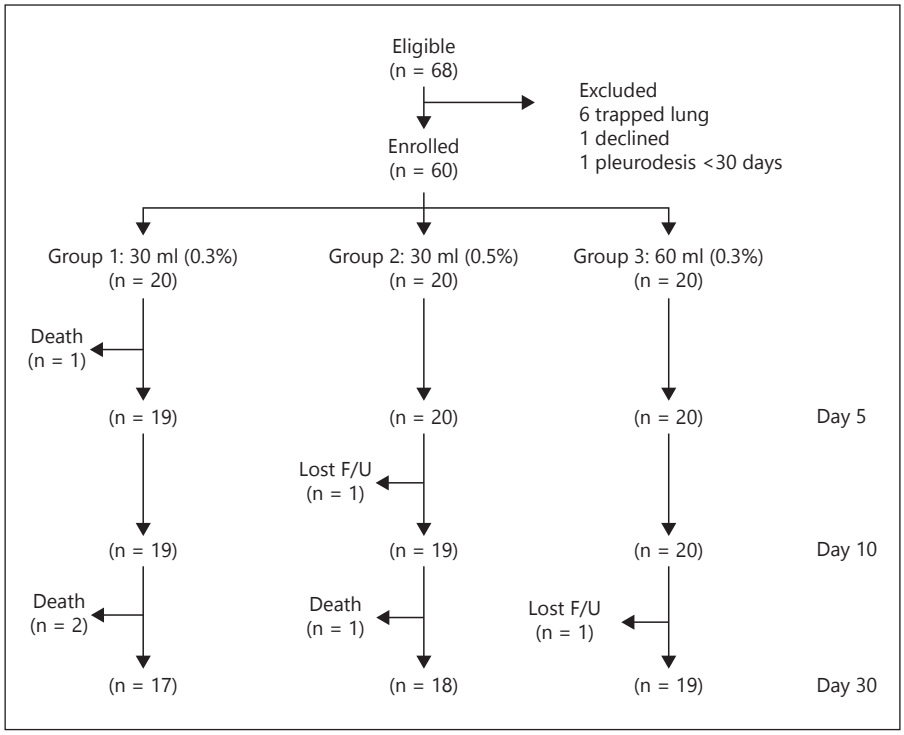

Fig. 1. Flow chart of the study design. F/U = Follow-up.

CTCAE v.4.0 [22, 23]. Serious and nonserious AE were our primary aim; therefore, we monitored clinical and laboratory parameters in the blood and vital signs, specifically heart rate, blood pressure, oxygen saturation and body temperature. In addition, patients were actively questioned both for worsening of preexisting conditions and/or symptoms and for the appearance of new symptoms. All events, new or worsening of preexisting conditions, were recorded. We opted to be conservative and not classify AE as related or unrelated to SN instillation. These patients had advanced disease, and for many symptoms it was difficult to adjudicate whether new events were related to pleurodesis or not.

Secondary outcomes were systemic inflammation, chest pain and efficacy of the procedure. We used serum C-reactive protein (CRP) levels as a surrogate marker for systemic inflammation and CRP was measured as a continuous variable. Chest pain was defined as a continuous variable according to the VAS results. Efficacy was evaluated according to two parameters: effusion recurrence and residual pleural cavity volume. Effusion recurrence was a binary variable defined as the need for additional pleural procedures during the follow-up period. The residual pleural cavity volume was defined as a continuous variable consisting of the difference between pleural cavity volumes measured by chest CT scans on days 5 and 30. The same radiologist specialized in thoracic radiology and blinded to group allocation performed all pleural cavity measurements. This measurement provided us with an objective evaluation of fluid reaccumulation.

Analysis

In each group, results before and after pleurodesis were compared using paired t or Fisher's test. The difference among groups was evaluated via Kruskal-Wallis or χ^2 test. Survival results were expressed using the Kaplan-Meier curve. Data were analyzed on an intention-to-treat basis, and missing data were evaluated for randomness and handled with mean imputation. For CRP and leukocyte curves, we used a model for the analysis of response profiles that assumed an unstructured correlation of data (until day 5) and evaluated time, group and the interaction between time and group. For all analyses, a value of $p < 0.05$ was defined as statistically significant.

Results

A flow chart of our trial design is depicted in figure 1. Table 1 presents demographic data. Documented complications defined according to CTCAE v.4.0 are shown in table 2. Overall, 199 AE were observed, and 23 of them were serious. There was no statistical difference between groups in terms of total AE occurrence ($p = 0.89$). Nevertheless, the serum creatinine level was more frequently increased in group 3 ($p = 0.02$). Logistic regression could reveal predictors for the occurrence of AE of grade 3 or higher.

The most frequent serious AE observed was hypoxia (table 2). One patient developed grade 4 hypoxia 2 days after pleurodesis. His chest radiography showed extensive bilateral alveolar infiltrates, and adult respiratory distress syndrome was diagnosed; he was intubated and re-

Table 1. Baseline characteristics of the patients

Characteristics	Group 1 (n = 20)	Group 2 (n = 20)	Group 3 (n = 20)	p
Age (mean ± SD), years	61.85±11.43	60.40±15.72	64.15±10.20	0.64
Gender, males/females	3/17	4/16	4/16	0.89
Median performance status (IQR)	50 (15)	60 (20)	55 (25)	0.09
Primary neoplasia				0.79
Breast	13	9	14	
Lung	3	6	4	
Ovary	1	2	0	
Unknown primary	1	1	1	
Other	2	2	1	
Median pleural fluid levels (IQR)				
LDH, U/l	344.5 (170)	263.5 (254)	281.5 (236)	0.66
Glucose, mg/dl	89 (47)	86 (40)	106 (34)	0.38
Protein, g/dl	4.5 (1.3)	4.1 (0.9)	4.3 (0.7)	0.35
Positive cytology, %	80	65	60	0.36

Group 1: 30 ml, 0.3%; group 2: 30 ml, 0.5%; group 3: 60 ml, 0.3%. Performance status = Karnofsky performance status; IQR = interquartile range (25–75).

mained under mechanical ventilation for 10 days; the patient fully recovered after this period. Most grade 3 hypoxia events (12 events) started 24 h after pleurodesis and were successfully managed with temporary O_2 nasal catheter (for a mean of 2 days). Only in 3 of the 12 cases, a specific cause for hypoxia could be established: pulmonary thromboembolism (1 patient) and severe (grade 3) pleuritic pain (2 patients). Acute kidney injury was also quite common, and, according to RIFLE criteria, these cases were classified as failure in 1 patient, injury in 7 patients and risk in 13 patients. Kidney injury was more frequent in group 3.

Four patients died during our study, 3 of them close to the last follow-up visit (day 30) clearly due to disease progression. Nevertheless, the other patient was a 63-year-old man with metastatic stomach adenocarcinoma. On the day following pleurodesis, his general condition deteriorated rapidly and he died on the next day. Despite our attempts to find the cause for this dismal outcome, the only AE found were an increase in serum creatinine and anemia (both of grade 1); however, the family declined autopsy, and therefore any further investigation was impossible. The official cause of death was sepsis followed by multiple organ failure.

After pleurodesis, both leukocyte counts and CRP levels were markedly increased, suggesting a significant systemic inflammatory reaction (fig. 2). Both parameters peaked around 3 days after pleurodesis and, for CRP, this increase was dose dependent (p = 0.005). Chest pain decreased progressively after drainage and pain levels did not differ among groups (p = 0.33; fig. 3).

The difference in the residual pleural cavity volume (day 30 vs. day 5; determined by CT scan) was small and did not differ across groups (table 3), suggesting that fluid reaccumulation was not radiologically significant. Indeed, only 2 patients had clinical recurrences: 1 patient within 9 days of the procedure and the other within 45 days; both patients belonged to group 3 (largest SN dosage).

On day 30, physical quality of life had improved in all groups, with no statistically significant difference (p = 0.52; table 3). The Kaplan-Meier survival curve (fig. 4) also revealed no significant difference among groups.

Discussion

In this study, hypoxia was the most common AE associated with SN pleurodesis, not only due to its frequency (21.6% of patients) but also due to its severity (grade 3/4). However, small variations in serum parameters without clinical relevance were mainly noted. The most common alterations were a decrease in red blood cell counts and increases in hepatic enzymes and creatinine. Only the increase in creatinine was dose dependent. Pleurodesis with SN was very successful at all the dosages used. This success, however, was accompanied by the development of intense systemic inflammatory reactions, which was reflected by the significant increase in leukocyte counts and

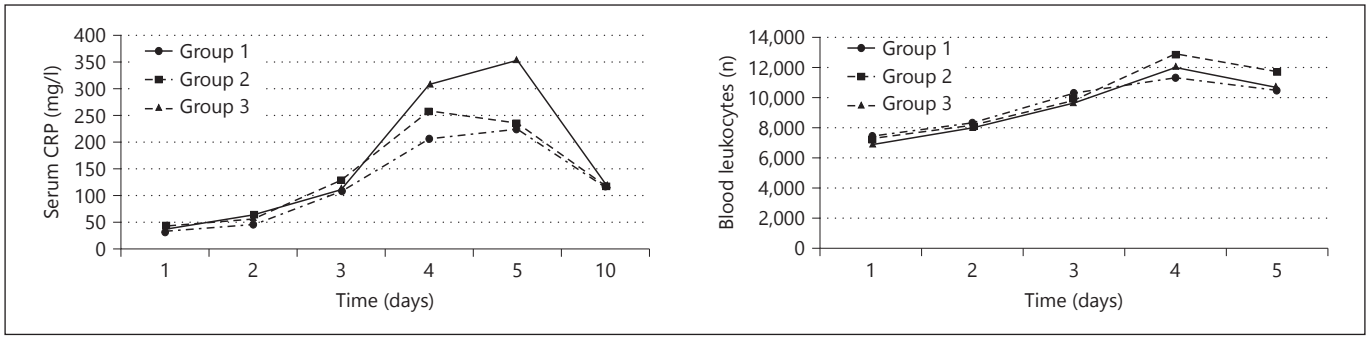

Fig. 2. CRP and leukocyte levels during the first 5 days of the study. Pleurodesis was performed on day 2. Response profiles showed significant intragroup and intergroup differences in CRP levels over time (p = 0.0001 and p = 0.005, respectively). There was intragroup serum leukocyte counts over time (p = 0.01), but there was no intergroup difference over time (p = 0.171).

Table 2. Adverse events

AE	Group 1	Group 2	Group 3	p
Patients who coursed with severe AE	7	6	8	0.89
Anemia				
Any event	14	12	15	0.69
Severe events	0	0	3	0.09
Creatinine increase				
Any event	5	4	12	0.02
Severe events	0	0	1	0.99
Hypoxia				
Any event	3	5	6	0.64
Severe events	3	4	6	0.62
Aspartate amino transferase increase				
Any event	7	3	8	0.20
Severe events	1	0	0	0.99
GGT increase				
Any event	5	6	5	0.99
Severe events	0	0	0	1.0
Nausea				
Any event	3	3	8	0.12
Severe events	1	0	0	0.99
Alanine amino transferase increase				
Any event	3	1	7	0.55
Severe events	0	0	0	1.0
Alkaline phosphatase increase				
Any event	3	1	5	0.26
Severe events	0	0	0	1.0
Hyperkalemia				
Any event	3	1	5	0.26
Severe events	0	0	0	1.0
White blood cell decrease				
Any event	2	3	2	0.99
Severe events	0	1	0	0.99
Fever				
Any event	2	3	2	1.0
Severe events	0	0	0	1.0
Hyponatremia				
Any event	2	3	2	1.0
Severe events	0	0	0	1.0
Pleuritic pain				
Any event	2	2	2	1.0
Severe events	1	1	0	0.99
Hypokalemia				
Any event	1	1	3	0.60
Severe events	0	0	1	0.99
Vomiting				
Any event	1	3	1	0.60
Severe events	0	0	0	1.0
Platelet count decrease				
Any event	1	0	1	0.99
Severe events	0	0	0	1.0
Thromboembolic event				
Any event	0	0	1	0.99
Severe events	0	0	1	0.99
Hypernatremia				
Any event	0	0	1	0.99
Severe events	0	0	0	1.0
Supraventricular tachycardia				
Any event	0	0	1	0.99
Severe events	0	0	0	1.0
Acute kidney injury				
Any event	0	0	1	0.99
Severe events	0	0	1	0.99
Soft tissue infection				
Any event	1	0	0	0.99
Severe events	0	0	0	1.0
Confusion				
Any event	0	0	1	0.99
Severe events	0	0	1	0.99
ARDS				
Any event	1	0	0	0.99
Severe events	1	0	0	0.99

Severe AE are events graded as 3 or 4 according to CTCAE v.4. The total numbers of AE observed are listed. Several patients had >1 AE. Fisher's test was used for comparisons between groups. ARDS = Adult respiratory distress syndrome.

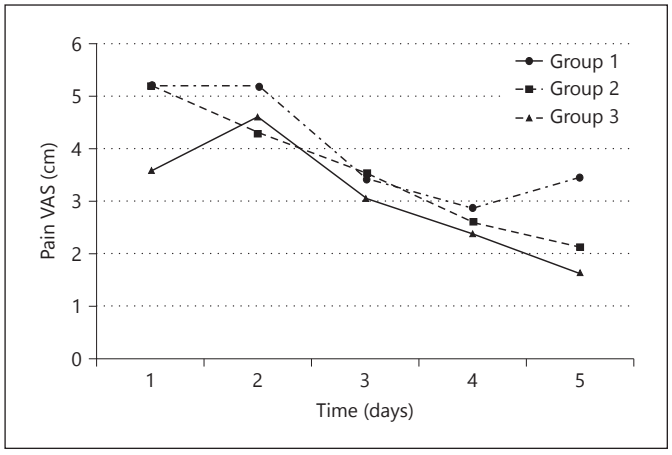

Fig. 3. Pain scores over the first 5 days of the study according to VAS. Pleurodesis was performed on day 2. Response profiles showed significant intragroup differences in pain scores over time (p = 0.049), but there was no intergroup difference over time (p = 0.22).

Table 3. Success rate and effectiveness of pleurodesis

Variables	Group 1	Group 2	Group 3	p
Clinical recurrence, n	0	0	2	0.60[c]
Difference in pleural fluid volume (days 30 vs. 5) on CT, ml[a]	33	–204	–84	0.52
Median difference in the quality of life (day 30 vs. before pleurodesis)[b]				
Physical	10.72	7.14	10.71	0.26
Psychological	–8.22	–12.5	–2.08	0.95
Social	–8.33	0	0	0.42
Environmental	–6.25	6.25	6.25	0.23
Mean follow-up, months	10.1	9.5	10.6	0.32

[a] Average differences between days 30 and 5 determined by CT (49 patients).
[b] Quality of life was evaluated in 51 patients.
[c] Fisher's test, the Kruskal-Wallis test was used for all other comparisons.

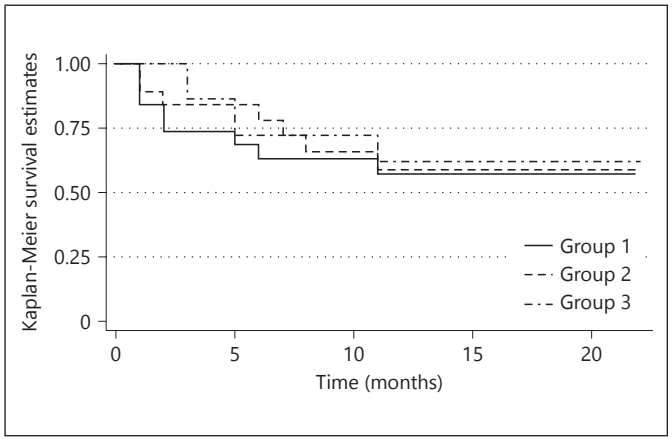

Fig. 4. Survival estimates, log-rank p = 0.88.

CRP levels in all groups, in an apparently dose-dependent manner, especially 3 days after pleurodesis.

Lung injury and respiratory distress have previously been described as complications of pleurodesis with several sclerosing agents [24]. Their etiology is uncertain and they seem to be associated with systemic inflammation and, in the case of talc, also to the size of the talc particle. In the Intergroup study, 6.2% of the patients developed respiratory failure [25]. Later, a multicenter cohort study using large-particle talc for pleurodesis did not report any patient with acute respiratory distress syndrome, but some patients developed mild respiratory symptoms and a small increase in oxygen use was required [5]. In our study, 21.6% of the patients had grade 3/4 hypoxia. We believe that two reasons might justify this high number of hypoxia cases. First, systemic inflammatory responses to SN were very intense, a fact which was also reflected by the significant increase in serum CRP levels. Second, our inclusion criteria were broad; we included patients with a performance status of 50–60, a known risk factor for lung injury [24]. We also believe that these factors might explain why some AE were observed in the present study and not in previous studies on SN [8, 9] and other sclerosing agents [1–7, 10].

Studies on other pleurodesis agents have not reported AE in such a systematic way, and therefore comparison is difficult. Still, the clinically relevant AE profiles of SN observed in this study seem comparable with other pleurodesis agents and consistent with the induction of a pleural inflammatory response invoked by the sclerosant. The frequent metabolic alterations were not previously described and are probably related to systemic consequences of SN instillation.

Pleurodesis is known to cause systemic inflammation [26], which can be monitored by CRP levels. We were not only able to demonstrate an increase CRP levels but also that this increase was dose dependent. This finding is interesting from a physiological perspective based on the knowledge that systemic inflammation peaks 48–72 h after SN instillation. Unfortunately, we could not find an association between peak CRP levels after pleurodesis

and the occurrence of metabolic alterations; however, the small number of patients limited the power of our model. All these facts prompt the search for safer strategies for MPE management. In a rabbit model, Tremblay et al. [27] were able to demonstrate that repeated pleural instillation of low SN doses were as effective as the standard regimen. This strategy could improve tolerability of SN pleurodesis. There is also a tendency to try entirely different approaches, e.g. the use of long-term indwelling catheters which release intrapleural drugs and has quality-of-life results similar to pleurodesis [28].

Our results can be generalized to patients with recurrent MPE in other tertiary institutions. Nonetheless, the small number of patients is a limitation of the study that could have precluded us to identify other pertinent AE. To be able to spot a significant difference in AE rates among groups, >130 patients have to be included in each arm. Moreover, the broad inclusion criteria may have led to overestimation of AE due to the inclusion of frail patients. Chemotherapy is another potential confounder in our study. Despite the fact that it was administered only 15 days after pleurodesis, a few of the late adverse events captured in this study could be actually secondary to chemotherapy rather than to pleurodesis.

In conclusion, hypoxia was the most significant adverse event after SN pleurodesis, but mild metabolic alterations were the most common. SN instillation causes considerable, dose-dependent, systemic inflammatory responses, therefore the patients' general status requires careful assessment, especially renal function and respiratory capacity, before treatment. SN pleurodesis was successful at all dosages tested. Consequently, for safety reasons, lower doses (0.3%, 30 ml) should be preferred. Future research should investigate whether even lower doses of SN can be used for pleurodesis in patients with MPE.

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