Safety Profile of the Use of Iodopovidone for Pleurodesis in Patients with Malignant Pleural Effusion

José Dias Andrade Neto^a Ricardo Mingarini Terra^b Rodrigo Maia Teixeira^a
Sylvana Vianna Pereira^a Paulo Manuel Pego-Fernandes^b

^aThoracic Surgery Division, Hospital Aristides Maltez, Salvador, and ^bThoracic Surgery Division, Heart Institute, University of São Paulo Medical School, São Paulo, Brazil

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Key Words

Pleural effusion · Pleurodesis · Povidone · Safety · Treatment outcome

Abstract

Background: Iodopovidone is an alternative agent used to promote pleurodesis in patients with malignant pleural effusion (MPE). However, safety is a concern, and many authors still reject its use. **Objectives:** Our main objective is to describe the occurrence of common and severe adverse events after pleurodesis with two different doses of iodopovidone in patients with MPE. Our secondary objective is to evaluate dose dependency, efficacy, quality of life, and systemic inflammation. **Methods:** We conducted a double-blind, randomized clinical trial including patients with recurrent MPE. Patients underwent chest tube insertion and were randomized into two groups according to the doses of iodopovidone: group 1 received 1% iodopovidone, and group 2 received 2% iodopovidone. During follow-up, adverse events, inflammatory markers, quality of life, and imaging exams were systematically evaluated and registered. **Results:** Sixty patients were analyzed (55 females, 5 males, median age 55.9 years). Overall, 227 adverse events possibly related to pleurodesis were registered, including 47 serious adverse

events (in 34 patients). Pleuritic pain and hypertensive peaks were the most frequently observed serious adverse events (11 and 10 episodes, respectively). Grade 3/4 metabolic events such as hyponatremia and an increase in alkaline phosphatase, AST and ALT levels were also common. C-reactive protein (CRP) levels increased substantially and peaked 48 h after pleurodesis. No difference was observed between groups with regard to adverse events, CRP levels, efficacy, or quality of life. **Conclusions:** Adverse events after iodopovidone pleurodesis in patients with MPE are common and similar in the two doses studied.

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Introduction

Chemical pleurodesis is a well-established treatment for recurrent malignant pleural effusion (MPE) [1]. Several sclerosing agents have already been tested, but nowadays, sterile talc is the most used agent because of its good efficacy when compared to other agents [1–3]. Nevertheless, talc pleurodesis is related to some severe complications such as hypoxia and acute respiratory distress syndrome [4–7]. These complications are less frequent after the use of talc with large particles [8–11]. Unfortunately, talc with

large particles is not widely available. Silver nitrate is another option, but again, previous studies have described frequent adverse events related to its use [12–14].

Iodopovidone has been reported as a good alternative to talc pleurodesis, with an efficacy rate around 90% and a low number of complications [15–19]. Moreover, it is easily obtained, easy to use, and inexpensive. However, its safety has not been systematically evaluated, and some clinicians reject its use because of reports of severe adverse events such as thyroid diseases, visual loss, and neurological disturbance [20–22].

Concerns over adverse events have been hindering the wider use of iodopovidone as a sclerosing agent. Indeed, the actual rate of such events is not known. Therefore, the objective of this study was to identify the adverse events related to iodopovidone pleurodesis in patients with MPE, classifying them according to the Common Terminology Criteria (CTC) grading system [23]. Furthermore, we aimed to evaluate the influence of iodopovidone dose on the incidence of such adverse events.

Methods

This was a double-blind, randomized, clinical trial that included patients with recurrent and symptomatic MPE, a radiography showing total or near-total lung expansion (>70%) after chest drainage according to two different raters, a Karnofsky performance status of >40, and documented informed consent. We excluded patients whose chest radiography after chest drainage did not show total or near-total lung expansion (>70%). We also excluded patients with hemorrhagic diathesis (prothrombin time <50% and a platelet count of <80,000/mm³), active pleural or systemic infection, neoplastic infiltration of the skin at the site of pleural catheter insertion, patients <18 years of age, presence of previous ipsilateral pleural interventions (with the exception of thoracentesis and pleural needle biopsies), an inability to understand the quality of life questionnaires, contralateral pleurodesis <30 days prior to the enrollment date, iodine allergy, and known thyroid disease. To undergo pleurodesis, patients should not have received chemotherapy in the previous 15 days, and, after pleurodesis, we postponed chemotherapy for 15 more days.

Data collection was performed at a tertiary institution. All participants signed the informed consent approved by our Institutional Review Board (CAPPesq 0710/11), and the study has been registered on clinicaltrials.gov with the number 01670786.

Definition and Classification of Adverse Events

We used the definition and classification of adverse events as proposed by the National Cancer Institute CTC for Adverse Events CTCAE version 4.0. The classification of adverse events according to their severity ranges from 1 to 5. Grades 1 and 2 are considered nonserious events and grades 3–5 serious events [23]. In addition, as suggested by the NCI guidelines of adverse events, we classified events as related or unrelated to the procedure [24].

With regard to frequency, we classified events as recommended by the Council for International Organizations of Medical Sciences (CIOMS), which defines common events as those that occur in 1–10% of exposed patients [25].

Sample Size and Group Randomization

We aimed to identify adverse events that would occur in at least 5% of patients undergoing iodopovidone pleurodesis (common events). Therefore, using proportion calculation, we came up with a sample size of 60 patients. With this amount, we have a power of 95% to detect events, with an incidence of ≥5%.

After having signed the informed consent, the patients were randomized and distributed into two groups by block randomization: group 1 received 1% iodopovidone solution, and group 2 received 2% iodopovidone solution. Investigators and patients were blinded to group allocation.

Procedures

Potentially eligible patients underwent pleural drainage with a chest tube (28 Fr) that was connected to a water seal system. After 24 h, lung expansion was evaluated by chest radiography, and patients who fulfilled inclusion criteria were referred for randomization. Pleurodesis was performed 48 h after chest tube insertion, and iodopovidone dose was administered through the chest tube according to group allocation. Those in group 1 received 100 ml of 1% iodopovidone solution, and those in group 2 received 100 ml of 2% iodopovidone solution. Lidocaine (2 mg/kg) was added to each solution. Patients who presented with severe pain received intravenous opioid analgesia during the procedure. After pleurodesis, patients remained in the hospital until their chest tubes were removed. During this period, they received oral analgesia with dipyrone, as well as codeine only in case of persisting pain.

Safety Analysis

We systematically sought adverse events through clinical, laboratory, and other complementary exams. Clinical evaluation involved the Visual Analogue Scale (VAS) for measuring chest pain, the UK Medical Research Council Dyspnea Scale (MRC), oxygen saturation, heart rate, arterial blood pressure, body temperature, and visual acuity. Laboratory and other complementary exams involved: a hemogram, C-reactive protein (CRP), tests of kidney and liver function, electrolytes, thyroid hormones, a chest X-ray, and an electrocardiogram. Most of these evaluations were performed immediately before pleurodesis and then on the 2nd, 4th, 10th, and 30th day after pleurodesis. All adverse events detected by clinical and complementary evaluation were registered and classified as serious and nonserious. We considered serious events those graded ≥3 according to the CTCAE version 4.0. Every patient was followed up from pleurodesis until death or the end of the study period.

Efficacy and Quality of Life Analysis

Efficacy was evaluated as a binary variable: success or failure, based on the need for further pleural procedures after pleurodesis. Recurrence of pleural fluid or the need for an additional pleural procedure 30 days after pleurodesis was considered as a failure. We considered recurrence when patients presented worse pleural effusion with worse symptoms.

For quality of life evaluation, patients were asked to answer the Portuguese language-validated World Health Organization Quality of Life BREF (WHOQoL-BREF) questionnaire preoperatively and 4 weeks after pleurodesis [26].

Fig. 1. Consort flowchart.

Statistical Analysis

Continuous variables with normal distribution were expressed as the mean and standard deviation, and differences between groups were calculated by Student's *t* test. Continuous variables with abnormal distribution were expressed as the median and interquartile range, and we used the Mann-Whitney test to compare groups. Categorical variables were compared by Fisher's or χ^2 tests. Analysis of repeated measurements was performed by ANOVA or the Friedman test. Survival results were expressed by the Kaplan-Meier curve. The data were analyzed using a statistical software program (version 21, SPSS, Chicago, Ill., USA), and $p < 0.05$ was considered statistically significant.

Results

Data for the study were collected from January 2010 to June 2013. In this period, 74 patients were considered eligible for pleurodesis, and 14 were excluded, as depicted in figure 1. Sixty patients were analyzed. Participants' demographic data are presented in table 1.

Overall, we observed 311 adverse events, 227 possibly related to pleurodesis, and 47 serious events within this last group, which occurred in 34 patients (table 2). Out of these, 25 patients had only 1 serious adverse event, 8 had 2 serious adverse events, and only 1 patient had >2 serious adverse events. Adverse event occurrence and distribution were similar across the two groups.

Pleuritic pain was the most common adverse event, occurring in 36 patients (60%) over the study period. When analyzing pleuritic pain possibly related to

Table 1. Demographic data

	Group 1	Group 2
Age, years	56.10±11.99	55.73±11.63
Sex		
Male	2	3
Female	28	27
Karnofsky scale, median (IQ)	60 (50–70)	60 (50–62.5)
Type of malignancy		
Breast	21	22
Lung	4	2
Others ¹	5	6
Histological diagnoses		
Positive	27	20
Negative	3	10
Pleurodesis side		
Right	18	15
Left	12	15
Pleural fluid analyses		
Number of cells	1,246.5±1,561.5	646±457
Lymphocytes, %	75.5±22.2	81.4±21.4
Neutrophils, %	16.5±20.5	14.5±20.6
LDH, U/l	674.9±588.2	864.8±782.0
Proteins, g/dl	4.36±0.96	4.38±1.11
Glucose, mg/dl	105.2±56.8	102.1±36.5

Data are means ± SD or numbers, unless otherwise indicated.

¹ Other malignancies were ovarian, uterus, lymphoma, head and neck carcinoma, as well as unknown etiology.

Table 2. Adverse events possibly related to pleurodesis

	Group 1	Group 2	p		Group 1	Group 2	p
Pleuritic pain				↑ Alkaline phosphatase			
Nonserious	11 (36)	11 (36)	0.93	Nonserious	13 (43)	15 (50)	0.55
Serious	6 (20)	5 (16)		Serious	7 (23)	3 (10)	
Hypertension				↓ Sodium			
Nonserious	15 (50)	16 (53)	0.34	Nonserious	2 (6)	6 (20)	0.26
Serious	7 (23)	3 (10)		Serious	3 (10)	5 (16)	
Hypotension				↑ AST			
Nonserious	1 (3)	2 (6)	0.49	Nonserious	11 (36)	6 (20)	0.26
Serious	0	1 (3)		Serious	1 (3)	2 (6)	
Pleural infection				↑ ALT			
Nonserious	0	0	1	Nonserious	7 (23)	6 (20)	0.26
Serious	0	1 (3)		Serious	1 (3)	0	
Tachycardia				↑ Bilirubin			
Nonserious	13 (43)	11 (36)	0.79	Nonserious	2 (6)	3 (10)	0.38
Serious	0	0		Serious	0	1 (3)	
Hypoxia				↓ Potassium			
Nonserious	2 (6)	3 (10)	0.81	Nonserious	0	0	1
Serious	0	0		Serious	0	1 (3)	
Hypothyroidism				Kidney injury			
Nonserious	4 (13)	1 (3)	0.35	Non-serious	3 (10)	5 (16)	0.54
Serious	0	0		Serious	0	0	
↑ Potassium				Anemia			
Nonserious	1 (3)	2 (6)	0.6	Nonserious	3 (10)	3 (10)	1
Serious	0	0		Serious	0	0	
Nausea							
Nonserious	0	2 (6)	0.49				
Serious	0	0					

Data are given as n (%). Nonserious = CTCAE grade 1/2; serious = CTCAE grades 3–5.

pleurodesis, it occurred in 33 patients (52.5%), including 11 serious cases (18.3%). Pain scores were higher during pleurodesis. Blood pressure changes were also frequent; most times, we observed hypertensive peaks, but we also registered hypotension in 1 patient classified as a serious event. Increased alkaline phosphatase, AST, and ALT were also common findings.

Visual analysis performed before and 2 days after pleurodesis did not show differences (Snellen scale means). Plasmatic CRP levels increased after iodopovidone instillation and peaked on the second day after pleurodesis, as shown in figure 2.

There were 2 pleurodesis failures within the first 30 days. One of them occurred in group 1 in a patient whose chest tube output remained very high for several days after the initial pleurodesis. He underwent talc pleurodesis and chemotherapy, and then the output decreased and the chest tube could be removed. The other failure occurred in group 2. In this case, the patient showed recur-

rence of the fluid that was also infected. A new pleural drainage procedure and antibiotics were necessary to control the situation. None of the other patients had recurrence of pleural effusion or needed an additional pleural procedure in the first 30-day period. The success rate was 96.6% in both groups.

On the 30th day, quality of life scores were similar to prepleurodesis scores, and there was no difference between the groups. The median survival was 4.3 months (range 2.5–6.14), with no statistical difference between the groups.

Discussion

In this study, we observed that adverse events after pleurodesis with iodopovidone in patients with MPE are common. We found a total of 227 events possibly related to pleurodesis in 60 subjects who underwent iodopovi-

Fig. 2. CRP analysis. Asterisks represent outlier values found in each dosage.

done pleurodesis. Although most of these events were classified as nonserious by CTCAE, 47 of them were considered serious, affecting 34 patients (56.6%). Moreover, we found that CRP levels peak 48 h after pleurodesis, suggesting a systemic inflammatory reaction after the procedure. Considering our sample and the doses tested, we did not find dose dependency in either the efficacy or occurrence of adverse events.

Pleuritic pain was the most frequent serious adverse event related to pleurodesis observed in our study. It occurred in 33 patients (55%) and was classified as serious in 11 of them (18%). Pain had already been reported as a complication of pleurodesis with iodopovidone as well as with other sclerosing agents [12–19]. Agarwal et al. [16] found a median VAS score of 50.5 (range 10–95) after iodopovidone pleurodesis through the chest tube in patients with MPE. Conversely, Olivares-Torres et al. [15] reported pain in only 5.8% of patients who underwent iodopovidone pleurodesis in their study. This better outcome might be explained by the following two factors: first, pain was not objectively measured; second, most patients underwent surgical pleurodesis under general anesthesia. Even though disturbing, most pain episodes in our study were limited to the first hours after iodopovidone instillation.

The second most frequent event observed in our series was blood pressure alteration. Forty-one patients developed hypertensive peaks after iodopovidone instillation, including 10 serious events, and 4 patients developed hypotension, including 1 serious event. Hypotension has already been reported after iodopovidone pleurodesis [15–17]; however, in previous studies, hypertensive peaks

have not been mentioned. In our study, many of these episodes were not associated with pain; therefore, we believe that most hypertensive peaks were due to procedure-related anxiety. In all cases, hypertension was self-limited and lasted a few hours. This finding supports blood pressure monitoring during pleurodesis.

Metabolic events as manifested by an increase in blood levels of alkaline phosphatase, AST and ALT, as well as a decrease in sodium were surprisingly common in our patients. This finding was not reported in previous series, probably because such alterations were not actively sought. It is challenging to come up with a reasonable explanation for such a finding; we speculate that it is associated with systemic inflammation triggered by the sclerosing agent. Indeed, our results support the argument that systemic inflammation occurs as a consequence of iodopovidone instillation. Within the first 24–48 h, we observed a steep increase in CRP levels, which peaked around 2–4 days after pleurodesis. Then, it slowly decreased until reaching baseline at around the 10th day. We have already reported similar alterations in another study with silver nitrate pleurodesis, suggesting that systemic inflammatory response is common with other sclerosing agents as well [14]. In addition, silver nitrate adverse events presented a dose-dependent relationship, which we did not find in the iodopovidone pleurodesis doses we used [14].

Thyroid function is a concern when using iodine therapies and whether iodopovidone pleurodesis interferes with this function is still a matter of debate [20, 27]. Yeginsu et al. [27] analyzed thyroid hormones 24 and 72 h after pleurodesis with iodopovidone in 12 patients with

MPE. They found no difference in these hormone levels over time. We measured hormone levels at baseline, on the 2nd and the 30th day after pleurodesis; 5 patients developed subclinical hypothyroidism as diagnosed by their thyroid-stimulating hormone levels. No medical treatment was necessary, and such events were considered nonserious events according to the CTCAE classification. Most of these hormone alterations were transitory and returned to normal values on the 30th day of analysis.

Other serious adverse events such as renal failure, mental confusion, and visual loss have been reported in the literature as a consequence of the use of iodopovidone [21, 22]; nevertheless, none of those events were observed in our series. This is an important factor because many physicians reject the use of iodopovidone as an alternative sclerosing agent due to the fear of such complications. It is important to underline the fact that mental confusion occurred after the use of high doses of iodopovidone as continuous irrigation for the treatment of mediastinitis in patients with renal failure, and that visual loss occurred after administration of extremely high doses of iodopovidone for pleurodesis. In spite of the fact that, in theory, these three severe adverse events might be very rare and our study might be underpowered to detect them, there is no evidence that these adverse events could happen in a normal pleurodesis scenario.

Our study has some limitations. First, it was very difficult to adjudicate which adverse events were truly related to pleurodesis. Patients with MPE have advanced disease, and many events could be a consequence of their frail status or disease progression and would probably occur even without pleurodesis. To minimize error, we correlated the time after pleurodesis and the type of event in our decision-making. Two different investigators rated the events, and disagreements were discussed until a consensus was reached. A second limitation of this study is that the small number of patients did not allow the detection of rare events. Unfortunately, the occurrence of more rare events will be detected only if larger case series are published.

Finally, our study population comprises a majority of breast cancer patients. This is a peculiarity of our hospital, and caution should be taken when generalizing our results for other tertiary cancer institutions. Pleurodesis in patients with breast cancer has a higher success rate when compared to other malignancies [28]. This could explain, in part, the very low number of recurrences in our series.

We observed a large number of adverse events. Nevertheless, this study has some characteristics which differ

from those of other similar analyses. Adverse events were prospectively collected, and we actively sought complications ordering lab tests that are not usually evaluated in clinical practice. Besides, even serious events actually had low clinical relevance, of which pain was the most common, and it was probably underestimated in other series. On top of that, in another study from our group [14], in which we used a similar methodology, we also found an unusually large number of adverse events after pleurodesis with silver nitrate as a sclerosing agent. Thus, although iodopovidone pleurodesis is associated with a high number of adverse events, it is not exclusive to iodine, and other agents also have high complication rates when actively looking for them.

Inflammatory response promoted by pleurodesis is described for the use of many sclerosing agents, and inflammation itself is probably the main cause of all these metabolic consequences [4–11, 14, 29]. We recommend a cautious approach with pleurodesis, whatever agent is used. Due to the concern over adverse events, we see a tendency to move to other strategies for the treatment of MPE as the use of indwelling pleural catheters [30, 31].

Conclusion

Adverse events after iodopovidone pleurodesis in patients with MPE are common; nevertheless, the majority of complications observed were transient pain and blood pressure alterations. As with other sclerosing agents, care should be taken, especially in patients with a bad performance status and many comorbidities.

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