Efficacy and safety of iodopovidone in chemical pleurodesis: A meta-analysis of observational studies

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Summary The search for an 'ideal' agent for pleurodesis continues. Iodopovidone is a topical antiseptic and has been shown to be safe and effective in many studies. The aim of this study was to evaluate the efficacy and safety of iodopovidone as an agent for chemical pleurodesis. We performed a systematic review of all the observational trials which have used iodopovidone for chemical pleurodesis. Six studies including 265 patients who had undergone chemical pleurodesis with iodopovidone were included for this analysis. Iodopovidone was used for variety of indications, which included pleural effusion (157 patients), and pneumothorax (108 patients). Pleurodesis was performed through tube thoracostomy in 144 patients and through thoracoscopy in 121 patients. The success rate of pleurodesis varied from 64.2% to 100%, and summary success rate of all the studies was 90.6% (95% confidence intervals [CI], 86.4–93.8). The success rate was independent for the procedure (tube thoracostomy [126/144; 87.5%, 95% CI 80.9–92.4] or thoracoscopy [114/121; 94.2%, 95% CI 88.4–97.6]) used for performing pleurodesis or for the indication (pleural effusion [139/157; 88.5%, 95% CI 82.5–93.1] or pneumothorax [101/108; 93.5%, 95% CI 87.1–97.4]). The only significant complication reported was chest pain of varying degree. Systemic hypotension was reported in three patients in only one study. There were no deaths related to chemical pleurodesis with iodopovidone. Overall, this review supports the safety and efficacy of iodopovidone as an agent for chemical pleurodesis in cases of recurrent pleural effusions and pneumothoraces regardless of their etiology.

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Introduction

Pleurodesis is a method to achieve a symphysis between two layers of the pleura in order to prevent accumulation of either air or fluid in the pleural space. 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 sclerosing agent through tube thoracostomy or through VATS. A plethora of chemical agents have been used for pleurodesis in the literature,1 and include talc,2 tetracyclines,3 quinacrine,4 antineoplastic drugs (bleomycin, mitomycin, nitrogen mustard),5 immunomodulating agents (interferon [IFN]-alpha and IFN-gamma),6,7 silver nitrate,8 biological agents (suspension of killed Corynebacterium parvum or Streptococcus pyogenes [OK 432]),9–11 and finally iodopovidone.12 An ideal sclerosing agent should have a high molecular weight and chemical polarity, low regional clearance, rapid systemic clearance, a steep dose-response curve, and should be well tolerated with minimal or no side effects.13 Such an ‘ideal’ agent remains undiscovered and the choice of a particular agent depends on the local availability and experience. The recently published International Survey of Pleurodesis Practice surveyed pulmonologists in five different English-speaking countries (USA, Canada, UK, Australia, and New Zealand) on their management of malignant pleural effusions, and found that talc was the agent of choice in 68% of the 859 respondents surveyed, followed by tetracycline derivatives and bleomycin (26% and 6%, respectively).14 Talc is cheap and readily available at many centers but serious concerns have been raised about the safety of talc. There are reports of acute respiratory distress syndrome following the administration of talc with many patients succumbing to the complication.15,16 We have recently analyzed our experience of chemical pleurodesis with iodopovidone in patients with both pleural effusion and pneumothorax, and found its efficacy rate of 89.1%.12 Although the first report of chemical pleurodesis with iodopovidone was published in 1991,17 it is only recently that interest has been rekindled in this agent because of its safety and easy availability. In view of the low cost and wide availability of this commonly used drug, it is important to analyze its efficacy and safety in large number of patients for recommending its widespread use. This systematic review is an attempt in this direction.

Material and methods

To identify the studies for inclusion in this review, all the authors independently searched the National Library of Medicine’s MEDLINE database for relevant studies published from 1966 till current date using free text terms: chemical pleurodesis, pleurodesis and/or iodopovidone, pleurodesis and/or betadine. Bibliographies of all selected articles and review articles that included information on iodopovidone pleurodesis were reviewed for other relevant articles. In addition, we reviewed our personal files. All the studies irrespective of language was identified. The abstracts of the studies were independently reviewed by two authors (RA and ANA), without blinding to study the details. Any disagreement was resolved by discussion between the authors. Data was recorded on a standard data extraction form.

The following items were extracted:

- Publication details (title; author(s); other citation details)
- Patient details
- Outcome measures (success rate of iodopovidone pleurodesis—defined as the absence of pleural fluid during follow-up)
- Complications related to the procedure

Statistical analysis

To calculate the efficacy of iodopovidone pleurodesis, we used binomial proportions in which the numerator was the success rate and denominator the total study population. The expected proportion was the success rate of each study included. We then calculated the 95% confidence intervals (CI) for the expected proportion using the Newcombe-Wilson method.18,19 The data from individual studies was then pooled, and a summary success rate with 95% CI was calculated. The difference between two proportions was assessed by the Chi-square test and the iterative method of Miettinen and Nurminen was used to construct the confidence interval for the difference between the proportions.18 Heterogeneity could be assessed only qualitatively by visual inspection of the Forest plot because of the study design of abstract patient data and inclusion of observational studies.20 The statistical package StatsDirect version 2.4.5 was used to perform the statistical analysis.

The institutional review board clearance was not required for this manuscript as this was a meta-analysis of observational studies.

Results

Our initial data search yielded a total of 1195 citations of studies that have used chemical
pleurodesis. We excluded 1185 articles by reviewing titles and abstracts as they did not involve pleurodesis with iodopovidone. We selected ten articles for our analysis. The inclusion criteria included the use of iodopovidone as an agent for pleurodesis, reporting the technique used for pleurodesis, the side-effects and the outcome of the pleurodesis. We also excluded case-reports. Of these ten articles, six met the inclusion criteria and were included in the analysis. 

Four studies were excluded as three of them were case reports and one was a letter to the editor. All the six studies were of observational nature. The characteristics of the patients and the methods used for pleurodesis are summarized in Table 1. Qualitative assessment of heterogeneity based on the amount of disparity among the individual point estimates and the degree of overlap among the confidence intervals was negligible (Fig. 1).

The total number of patients in all the studies included 265 patients. Iodopovidone was used for variety of indications, which included pleural effusions (157 patients), and pneumothorax (108 patients). The pleural effusions were mainly malignant effusions, and the pneumothorax was spontaneous, both primary (where the underlying lung is healthy) and secondary (where the pneumothorax occurs as a complication of some underlying pulmonary disease). All the studies were single center except the study by Olivares-Torres et al., which was multi-centric. Tube thoracostomy was used in 144 patients and thoracoscopy in 121 patients.

There were no deaths related to chemical pleurodesis with iodopovidone. The reported complications of iodopovidone pleurodesis include chest pain and systemic hypotension (three patients in the study by Olivares-Torres et al.). The occurrence of chest pain has been described to a varying degree by different authors with one study describing it as a universal occurrence. However,

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient (n)</th>
<th>Diagnosis</th>
<th>Method of pleurodesis</th>
<th>Success rate n [%]; (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1)</td>
<td>15</td>
<td>Malignant pleural effusion</td>
<td>Tube Thoracostomy; iodopovidone with normal saline</td>
<td>15 [100]; (81.9–100)</td>
</tr>
<tr>
<td>(2)</td>
<td>39</td>
<td>Malignant pleural effusion</td>
<td>Tube Thoracostomy; iodopovidone with normal saline</td>
<td>33 [84.6]; (69.5–94.1)</td>
</tr>
<tr>
<td>(3)</td>
<td>14</td>
<td>Malignant pleural effusion</td>
<td>Tube Thoracostomy; iodopovidone with normal saline</td>
<td>9 [64.3]; (35.1–87.2)</td>
</tr>
<tr>
<td>(4)</td>
<td>52</td>
<td>Pleural effusion (44 malignant, 8 non malignant)</td>
<td>Tube Thoracostomy (12); Thoracoscopy (40); Iodopovidone with normal saline</td>
<td>50 [96.2]; (86.8–99.5)</td>
</tr>
<tr>
<td>(5)</td>
<td>81</td>
<td>Spontaneous pneumothorax</td>
<td>Thoracoscopy; iodopovidone hydroalcoholic solution</td>
<td>76 [93.8]; (86.2–97.9)</td>
</tr>
<tr>
<td>(6)</td>
<td>64</td>
<td>Pleural effusion (36 malignant, 1 non-malignant) Spontaneous pneumothorax (27)</td>
<td>Tube Thoracostomy; iodopovidone with normal saline</td>
<td>57 [89.1]; (78.8–95.5)</td>
</tr>
</tbody>
</table>

*Non-English, CI confidence intervals.
none of the studies have measured pain systematically except the study by Agarwal et al.\textsuperscript{12} where the authors have used Visual Analog Scale for measurement of pain.

The success rate was not significantly different whether tube thoracostomy (126/144; 87.5%, 95% CI 80.9–92.4) or thoracoscopy (114/121; 94.2%, 95% CI 88.4–97.6) was used for pleurodesis \[ P = 0.06 \] or whether the etiology was pleural effusion (139/157; 88.5%, 95% CI 82.5–93.1) or pneumothorax (101/108; 93.5%, 95% CI 87.1–97.4) \[ P = 0.17 \].

### Discussion

Chemical pleurodesis is a well-accepted therapy for patients with recurrent pleural effusions and pneumothorax, either with tube thoracostomy or thoracoscopy. The question is the choice of the sclerosing agent, which is not only determined by the efficacy of the agent but also by its cost, accessibility, safety, ease of administration and the number of administrations to achieve a complete response. In a review of English literature from 1966 to 1994, which included 1168 patients, teflan was the most effective chemical agent for malignant pleural effusions, with a complete success rate of 93% compared with \textit{Corynebacterium parvum} (76%), tetracycline (67%), doxycycline (72%) and bleomycin (54%).\textsuperscript{3} Furthermore, in 32 case series of 723 patients of predominantly malignant effusions, talc was effective either completely or partially in 659 (91%) of cases.\textsuperscript{2} In a meta-analysis,\textsuperscript{26} talc was found to be the most effective agent for pleurodesis, and thoracoscopic pleurodesis the preferred technique for pleurodesis based on efficacy. There was no evidence for an increase in mortality following talc pleurodesis. Still, there are serious concerns about the safety of talc. Talc is known to cause systemic embolization, and is a potential cause of ARDS and respiratory failure.\textsuperscript{15,16} Moreover, pharmaceutical talc (Steri-talc) with well-described limits\textsuperscript{25} is not readily available in many countries including India, and there have been attempts in even using non-pharmaceutical talc for pleurodesis.\textsuperscript{27}

Iodopovidone is a topical antiseptic and has been shown to be safe and effective in several studies.\textsuperscript{12,23} The precise mode of action of iodopovidone remains unclear, but it leads to enhanced pleural fibrosis which may be related to the low pH (pH, 2.97) of the sclerosing solution,\textsuperscript{23} or to the strong oxidative and cytotoxic properties of iodine that can induce a potent inflammatory response.\textsuperscript{28} Also iodopovidone has anti-exudative properties which may be related to the chelation of proteins.\textsuperscript{29} Theoretically the mechanism could also be similar to that described recently for talc i.e. production of fibroblast growth factor.\textsuperscript{30}

Meta-analysis is a statistical procedure that integrates the results of several relevant independent studies, and allows one to arrive at a common conclusion from an entire body of research. It provides a more precise estimate of a treatment effect, and may explain heterogeneity between the results of individual studies.\textsuperscript{31} Although generally applied to randomized controlled trials, a growing number of meta-analyses of observational studies in epidemiology (MOOSE) have appeared in the literature.\textsuperscript{32,33}

We therefore used the MOOSE methodology,\textsuperscript{32} and pooled the data on the efficacy and safety of chemical pleurodesis with iodopovidone. In our study, we assessed heterogeneity by visual inspection of the Forest plots in absence of any valid described technique to describe heterogeneity in abstract patient data observational study meta-analyses. Visual inspection of Forest plots to assess study heterogeneity is useful even when formal statistical tests fail to detect significant heterogeneity, as these statistical tests are underpowered to detect clinically important heterogeneity, especially when the number of outcomes, number of patients, or number of trials is modest. Moreover, it is important to avoid concluding that no heterogeneity exists among studies by relying solely on statistical tests.\textsuperscript{20}

The summary success rate of iodopovidone pleurodesis in our study was 90.6%, which is almost equal to the efficacy of talc pleurodesis (93%)\textsuperscript{2} and other inexpensive agents used for chemical pleurodesis which include silver nitrate (75–90%) and quinacrine (64–100%).\textsuperscript{34} The efficacy of iodopovidone was regardless of the etiology (pleural effusion vs. pneumothorax) or the technique (tube thoracostomy vs. thoracoscopy) used for performing pleurodesis. Importantly, talc causes lung injury with more than 35 cases of ARDS related to talc reported in the literature;\textsuperscript{15} iodopovidone, on the other hand is associated with minimal side effects although the experience with iodopovidone vis-à-vis talc is minimal.

The only significant side effect of iodopovidone is the occurrence of chest pain, which has been described to a different degree in various studies. The most likely reason for this is because of different procedures used for performing the pleurodesis (tube thoracostomy vs. thoracoscopy). The studies that have employed thoracoscopy have patients who are already receiving anesthesia where pain measurement is likely to be fallacious.
Moreover, except in one study, none have systematically assessed the occurrence of chest pain. Hypotension was reported by only one study that too in only three patients. It is not clear whether the hypotension was an anaphylactoid reaction or pain-associated vasovagal reaction. However, iodine can cause severe allergic reactions, especially in patients with allergic diathesis, and thus one should be prepared to deal with this emergency. Finally, iodine may also precipitate thyrotoxicosis in patients with subclinical hyperthyroidism (Jod-Basedow effect).

In conclusion, iodopovidone is an effective, safe, readily available, and inexpensive alternative to achieve chemical pleurodesis in cases of recurrent, pleural effusions and pneumothoraces regardless of their etiology.

References