OUTPATIENT TALC ADMINISTRATION BY INDWELLING PLEURAL CATHETER (IPC) FOR MALIGNANT EFFUSION (IPC-PLUS)

NEJM / 2018

THE CLINICAL QUESTION

Is talc administered through an indwelling pleural catheter more effective at inducing pleurodesis than the use of an indwelling pleural catheter alone?

TAKE HOME MESSAGE

IPC-Plus demonstrated MPE without substantial lung entrapment treated with IPC had a greater chance of pleurodesis when talc administration was part of the treatment protocol than when the IPC alone, without any deleterious effects.

BACKGROUND

Malignant pleural effusion (MPE) is a commonly encountered clinical problem. Management of MPE traditionally involved chemical pleurodesis that usually required an inpatient stay of 4-7 days. Alternatively, IPC has been shown to manage patient symptoms just as well as talc pleurodesis with reported spontaneous pleurodesis rate of 16-65%. In a prior study that applied talc through an IPC to achieve pleurodesis as an outpatient protocol, the success rate was 92%.

This trial examens if a combination of IPC and chemical pleurodesis with talc increases the possibility of pleurodesis as compared to IPC alone.

STUDY DESIGN

Type of trial: multicenter, randomized, placebo-controlled, single-blinded, parallel-group trial
Study groups: IPC with placebo vs. IPC with Talc Slurry

Settings: 18 secondary and tertiary centers in UK

Enrollment: 154 underwent randomization
76 to IPC-placebo group (70 included for intention to treat analysis)
78 to IPC-talc group (69 included for intention to treat analysis)

Treatment period: Patients underwent IPC placement and maximal fluid drainage(day 1) after enrollment. As outpatients, they had a minimum of three further drainages, limited to 1 liter each, followed by assessment at day 10 for trapped lung based on CXR (< 75% pleural apposition) or thoracic US (> 1/3 opacification) post-maximal drainage.

Patients without trapped lung underwent randomization.

Follow up: Patients were followed for trial outcomes until 70 days after randomization or until death (whichever occurred first).

Primary outcome
- Proportion of participants with successful pleurodesis at day 35 after randomization.

Secondary outcomes
- Successful pleurodesis (day 70)
- quality-of-life scores (QLQ-C30 and EQ-5D-5L)
- Symptom scores for chest pain and dyspnea
- Hospital days

Intervention
- Patient deemed suitable underwent a dose of intrapleural lidocaine, adjusted for body weight, before the administration of placebo or talc through an opaque syringe to maintain blinding.
- Placebo group received 50 mL of intrapleural sodium chloride, 0.9% solution through the indwelling pleural catheter.
- Talc group received 4 g of sterile, graded talc slurry with 50 ml of sodium chloride 0.9% solution through the indwelling pleural catheter.
- Participants were discharged after a 2-hour minimum period of observation, and the next drainage took place between 12 and 36 hours after the administration of talc or placebo.
- Subsequent drainage frequency was determined by the local investigating team (at least twice per week for the duration of the trial)

POPULATION

Inclusion criteria
1. Symptomatic malignant pleural effusion, agreed at appropriate local / regional MDT to require IPC, defined as pleural fluid in the context of
   a. Histologically proven pleural malignancy
   b. Otherwise unexplained pleural effusion in the context of clinically proven cancer elsewhere
   c. Radiologically proven pleural malignancy as diagnosed in normal clinical practice on thoracic CT in the absence of histocytological proof
2. Expected survival greater than 2 months

Exclusion criteria
1. Age < 18 years.
2. Females who are pregnant or lactating.
3. Previous attempts at pleurodesis on same side as effusion requiring management.
4. Previously documented adverse reaction to talc or lidocaine.
5. Community services unable to drain indwelling pleural catheter at least twice per week.
6. Evidence of extensive lung entrapment on CXR or CT, or significant fluid loculation on ultrasound scan, to a level which would normally be a contraindication to attempted talc pleurodesis or IPC insertion.
7. Other contraindication to indwelling pleural catheter insertion

Baseline Characteristics
- Evenly distributed in age, sex, cancer type, drainage prior to enrollment. With regarding to treatment at baseline, placebo group had more patients on oral glucocorticoid (13 vs 7). NSAIDS (14 vs 11). and LMWH (12 vs 4) as compared to the Talc group. Talc group had more patients who recieved radiotherapy (19 vs 14) and chemotherapy (15 vs 6) than placebo group.

OUTCOMES

Primary outcomes:
- Successful pleurodesis (day 35): 30 of 69 patients (43%) in the IPC-talc group compared with 16 of 70 (23%) in the placebo group (P = 0.008)

Secondary outcomes:
- Successful pleurodesis (day 70): 35 of 69 patients (51%) in the IPC-talc group compared with 19 of 70 (27%) in the placebo group (P = 0.003).
- IPC-talc group had better quality-of-life scores (QLQ-C30 and EQ-5D-5L) than IPC-placebo at all time points. Mean difference across trial for QLQ-C30 score was 6.9 points (P = 0.02) and EQ-5D-5L score was 0.07 points (P = 0.04).
- IPC-talc group had better symptom scores at all assessment points during the trial. Estimated treatment effects for talc of -5.7 points (95% CI, -9.8 to -1.6) for chest pain (P = 0.007) and -5.6 points (95% CI, -8.5 to 1.3) for dyspnea (P = 0.15).
- Hospital days until day 70 was 4.1±7.9 days in the IPC-talc group and 3.0±5.2 days in the IPC-placebo group (P = 0.74)

Adverse events:
No significant difference between the IPC-talc vs. IPC-placebo.
- Blockage of the IPC: 5 of 78 (6%) in IPC-talc vs. 3 of 76 (4%) in IPC-placebo

COMMENTARY

Study Strength:
Well-designed randomized, placebo-controlled, multicenter, single blinded (patient) trial for assesment of IPC-Talc for pleurodesis management of MPE. This is the first study of its kind to address several points:
- IPC-talc pleurodesis can be done safely as an outpatient procedure; thus, reducing need of hospitalization with traditional talc pleurodesis.
- IPC-talc pleurodesis success rate is 43% at 35 days post-randomization.
- IPC-talc does not show increased catheter clogging incidence.

Study Limitations
- IPC-talc group had more patients at baseline with radiation and chemotherapy (which may improve underlying disease)
- IPC-placebo group had more patients at baseline with oral glucocorticoids and NSAIDS(which may impede pleurodesis)
- IPC drainage schedule during trial was not standardized.
- Effect of IPC-Talc cannot be assessed beyond 70 days.
- Pleurodesis success is when two objective criteria were met (1. < 50 ml of fluid was drained on 3 consecutive occasions. AND 2. CXR after drainages shows < 25% opacification of hemithorax). This may not be the most accurate way to assess pleural adhesion.

Future study questions:
- Cost analysis of IPC-talc should be assessed to see if the IPC-plus protocol can save healthcare dollars (IPC-Talc compared to IPC-placebo) and IPC-Talc compared to traditional talc pleurodesis).
- Is there another agent that can be more or equally effective (ie. IPC-talc vs. IPC-Povidone Iodine vs. IPC-Silver Nitrate)?
- Can you combine IPC-plus and ASAP trials (ie. IPC-plus with daily drainage) to see if there is an increased pleurodesis effect)?

FUNDING

Unrestricted research grant from Becton Dickinson - also supplied PleurX catheters and drainage bottles for all the participants

SUGGESTED READING

1. Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. JAMA 2012;307: 2383-9.2.
2. Wahidi MM, Reddy C, Yarmus L, et al. Randomized trial of pleural fluid drainage frequency in patients with malignant pleural effusions: the ASAP Trial. Am J Respir Crit Care Med 2017;195:1050-7.3.
3. Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. JAMA 2012;307: 2383-9.

ARTICLE CITATION

Bhatnagar R, Keenan EK, Morley AJ, Kahan BC, Stanton AE, Haris M, et. al. Outpatient Talc Administration by Indwelling Pleural Catheter for Malignant Effusion. N Engl J Med. 2018;378(14):1313-1322.

If you would like to become a reviewer for the "**ABIP Journal Club**," Please contact **Christian Chattas** at **christian.ghattas@osumc.edu**