Peer Review File

Article information: http://dx.doi.org/10.21037/tcr-22-1203

Reviewer A

General Comments:
The authors describe a multicenter, though small, single-arm cohort study using a fibrin sealant via a novel device that allows for such injection after percutaneous lung biopsy. In association with the growing literature on such approaches, the authors are to be commended on this work to attempt to improve the safety of this procedure. Although this data is certainly hypothesis-generating, I would recommend that the manuscript be reworded in sections (especially the Discussion section, as described below) to avoid too forcefully stating that this approach will limit complications and reduce costs; supportive data for these statement awaits larger studies with comparison arms. This is primarily a safety and feasibility study. Additionally, it would be useful to know more about the patients who underwent this procedure, especially underlying lung disease that would have affected the risk of pneumothorax.

Major Comments:
1. In order to potentially strengthen the findings of the study, it would be useful to have a control group; this could be done retrospectively via collection of data on similar patients who underwent PLB at the institutions prior to this study, or potentially during the trial period, who did not undergo glue administration.
Reply 1: We added some yet unpublished retrospective data collected from two out of three investigational sites involved in the trial, related to similar patients who underwent PLB at their institutions prior to or concurrently with this study. (See page 15, line 368-371).

2. It would also be useful to describe any prior experience, including especially any training or run-in period that the operators had, before implementing use of the MIPP-Kit during the study.
Reply 2: We added the training information into main text. (See page 8, line 192-194).

3. Please comment in greater detail on how the amount of glue to be delivered was chosen, and whether there were any specific differences in the number of pneumothoraces based on dosage. (Page 8, Lines 187-188) Additionally, please provide an explanation for why a larger amount of BioGlue was routinely used at one of the sites (Bari).
Reply 3: We added more information into main text. (See page 8, line 188-191). An hypothesis about the larger amount of BioGlue used in Bari could be that all the enrolled patients requiring the use of the largest MIPP-kit (MIPP-KIT-PNX15; 17.5%) and the 5ml syringe of BioGlue (15%) were enrolled there, thus potentially increasing the residual BioGlue amount due to the size of introducer.

4. Table 1 and Results: In my opinion, it would be important to report the number of patients

with medical comorbidities that could lead to increased risk of post-procedural pneumothorax (hx asthma, hx COPD, hx ILD, prior hx pneumothorax) or bleeding (anticoagulant use, antiplatelet agent use, coagulopathy, pulmonary hypertension). Also, is it relevant to report the number of patients with allergies in the Results section? The authors have already excluded those with allergies to the study drugs from their cohort.
Reply 4: We supplemented Table 1 with the number of patients with medical comorbidities that could lead to an increased risk of post-procedural PNX or bleeding (See Table 1).
The reporting of patients with allergies (not related to the investigational product) was intended to better describe the enrolled population.

5. In the discussion, the authors make the argument that the MIPP kit PNX device reduces complications and is "very likely" associated with a "sizeable healthcare cost impact." While these possibilities are certainly reasonable discussion points to bring up, this current study is a very small sample size with a single arm (no control group) and no cost analysis. The discussion regarding other studies is well-written, and the authors would do well to limit their conclusions about the current device from the current study to hypothesis-generating. See Page 14-15, Lines 335-344. For example, we really do not have a strong idea of the "effect" of the MIPP kit (Page 14, Line 335), only the descriptive statistics described. The wording elsewhere should mimic what the authors wrote in the Limitations section (Page 15, Lines 362-364)
Reply 5: We rewrote the section according to the indication of the reviewer (See page 14, line 344, 347-349.

6. Discussion, Page 15, Lines 346-355: I believe I understand the purpose of this paragraph, but it is a bit unclear. Are the authors suggesting that the use of glue prevented complications from worsening in those who had already developed pneumothorax or bleeding after biopsy? Perhaps this could be made more explicit to the reader: "The lack of "Post-Glue" complications in the "Pre-Glue" complication group suggests that the use of a surgical sealant with MIPP kit PNX device may have prevented such complications from worsening, despite the high risk inherent in such patients." (or words to that effect)
Reply 6: We rewrote the section according to the comment of the reviewer (See page 15, line 358,359).

Minor Comments:
Abstract, Line 41: "developed" in place of "had", likewise insert "developed" before "pulmonary hemorrhage"
Reply: we changed it (See page 2, line 40).

Page 4, Line 85: "PTX" is the more common acronym used for pneumothorax in English medical literature; consider using this in place of "PNX", though understanding that the device in question has PNX in its name.
Reply: We elected to maintain PNX as an acronym, even if it is a less common one, not just considering the name of the device, but mostly since in PubMed many articles are using the PNX acronym for pneumothorax.

Page 4, Line 86: “reported” in place of “registered”
Reply: we changed it (See page 4, line 86).

Page 4, Line 97: “Though” in place of “Despite”
Reply: we changed it (See page 4, line 97).

Page 5, Line 106: “and” before “hepato-biliary”
Reply: we changed it (See page 5, line 106).

Page 5, Line 107: remove additional space before “in several”
Reply: we changed it (See page 5, line 107).

Page 5, Line 110: “us” before “to investigate”
Reply: we changed it (See page 5, line 110).

Page 5, Line 112: “Conformite Europeanne (CE)” in place of “CE”
Reply: we changed it (See page 5, line 112).

Page 5, Line 114: recommend brief description of these “other indications” rather than merely citing the sources
Reply: we added the description (See page 5, line 114-116.

Page 6, Line 138: “in” in place of “to”
Reply: we changed it (See page 6, line 138).

Page 6, Line 149: “patient’s” in place of “patient”
Reply: we changed it (See page 6, line 149).

Page 8, Line 194: “severity” in place of “seriousness”
Reply: we changed it (See page 9, line 200).

Page 9, Line 200: “were not required” in place of “had not”
Reply: we changed it (See page 9, line 206).

Page 9, Line 205: “post-procedure duration of hospitalization” in place of “hospitalization duration after them”
Reply: we changed it (See page 9, line 211).

Page 9, Line 216: remove “from it”
Reply: we removed it (See page 9, line 223).

Page 10, Line 231: remove additional space before “serious”
Reply: we removed it (See page 10, line 238).

Page 11, Line 231: remove additional space before “with”
Reply: we removed it (See page 11, line 255).

Page 11, Line 250: add “right” before “middle”
We added it (See page 11, line 258).

Page 11, Line 263: “arterial embolization” in place of “artherial embholization”
Reply: we changed it (See page 11, line 271).

Page 12, Line 268: “occurred” in place of “occured”
Reply: we changed it (See page 12, line 276).

Page 12, Line 277: “with” in place of “showing”, remove “” around no complication
Reply: we changed it (See page 12, line 286).

Page 12, Line 278: “respectively” in place of “rispectively”
Reply: we changed it (See page 12, line 287).

Page 13, Line 311: “provides” in place of “is providing”
Reply: we changed it (See page 13, line 320).

Page 13, Line 315: “the risk” in place of “the one”
Reply: we changed it (See page 14, line 324).

Page 14, Line 330: remove additional space before “in one instance”
Reply: we removed it (See page 14, line 339).

Page 16, Line 368: “support” in place of “suport”
Reply: we changed it (See page 16, line 386).

Table 2: Recommend changing title to something like: “Radiographic and Procedural Characteristics”
Reply: we changed it (see Table 2).

Table 2: Recommend changing “Regime of Biopsy” to “Location of Biopsy Procedure”
Reply: we changed it (see Table 2).

Table 2: insert comma after “Device”
Reply: we added it (see Table 2).

Table 2: resize to avoid a second page, so that Total (N=40) is not included again on 2nd page
Reply: we changed it (see Table 2).

Table 4: Recommend changing “Regime of Biopsy” to “Location of Biopsy Procedure” in the title, in Row 4, and in legend.
Reply: we changed it (see Table 4).

Table 4: Difficult to read columns due to sizing, please resize and make sure to check PDF formatting during submission
Reply: we changed it (see Table 4).

Table 5: Cost impact would be inferred and is more appropriate for the discussion than in the title of this figure. Recommend changing to something like: “Length of hospital stay after percutaneous lung biopsy using MIPP-Kit PNX, based on investigational site.”
Reply: we changed it (see Table 5).

Reviewer B

This study evaluated the safety of the new percutaneous lung biopsy technique using a MIPP kit PNX device and BioGlue. In 40 patients who underwent percutaneous biopsies, three complications (2 pneumothoraces and one pulmonary hemorrhage) occurred after glue injection during percutaneous lung biopsy. The new technique using new devices seems to be promising in terms of safety. My comments are as follows:

Comments:
1. Please add a figure of MIPP-Kit PNX.
Reply 1: We added a figure of the MIPP-Kit PNX used to inject the surgical adhesive after CT-guided interventional thoracic procedures (see new Figure 1)

2. Please add figures of the procedure of the current PLB technique.
Reply 2: We added a figure of the MIPP-Kit PNX used to inject the surgical adhesive after CT-guided interventional thoracic procedures (see new Figure 1)

3. Please describe the manufacturer of the MIPP-Kit PNX. Are they prototype instruments? Or are they available in the market in Italy?
Reply 3: As described in the introduction, the MIPP-Kit is a CE-marked tool with a dual-lumen catheter designed to facilitate the optimal application of fibrin sealants after diagnostic and therapeutic percutaneous procedures and is commercially available. The MIPP-KIT-PNX10 and MIPP-KIT-PNX15 (variations of the device to be used in lung biopsies) are not yet marketed in Italy.

4. This is merely a non-comparative single arm study. So, don’t use strong phrases such as “very promising preliminary results (line 44),” “this study is providing initial but strong evidence (line 311),” “very low incidence of adverse events (line 337),” and “it is very likely associated with a sizeable healthcare cost impact (line 338).”
Reply 4: We rewrote the sections according to the indication of the reviewer (See line 44, line

344, line 347, line 349).

5. Please describe the final diagnosis of the target lesions.
Reply 5: We have not captured this information in the CRF, given the intended use of the device and the objective of the trial.

6. Please describe the diagnostic yield of PLB.
Reply 6: See previous answer.

7. How many specimens per patient were obtained?
Reply 7: This information was not captured in the CRF, only the duration of the procedures.

8. Did you use rapid on-site cytologic evaluation?
Reply 8: See answer to #5, above.

9. Table 1. The line "ECOG Performed, N (%)" is not necessary.
Reply 9: The line was removed (see Table 1).

10. Table 2. The line "Type of BioGlue, N (%)" is not necessary.
Reply 10: We feel that the line can be useful to understand the amount of BioGlue required for the procedures, so we elected to keep it.

Reviewer C

In this study, the authors piloted the safety and efficacy of a new device "MIPP Kit PNX" in preventing percutaneous lung biopsy complications. This is well conducted study and well written and will be of valuable to the medical literature. However, I have few suggestion and comments for the authors to consider.
Please note that the authors/editor are free to have their own discretion/judgment either to consider or disregard my opinion/comments/suggestions expressed in this review and also to take into consideration of other reviewers opinion and comments regarding this manuscript. Please also consider to disregard my review and consider another reviewer if you consider to be appropriate.
Comments to the authors
This is a well conducted study and well written article and I don't see any major flaws or issues. Few minor suggestions/comments though for some clarity.
(a) Title – I think the "MIPP kit PNX" should be written in full not abbreviated. Most will not know what "MIPP kit PNX" means. Also what does "PNX" stand for "pneumothorax" ? . I did try my google friend with no success, when I ask google to show what is "MIPP kit PNX" – and notice for "MIPP kit PNX" only track pants, mechanical tool sets, including children play toys are coming up for results.
Reply a):We did not change the acronym of the device in the title, but we spelled it out and clarified it in the abstract (see page 2, line 34 and line 35). Please also note that PNX is one of

the most widely used acronyms of pneumothorax in the scientific literature (see PubMed).

(b) Affiliation - In some it is written as “(ITA)” and others as “(Italy)” – I assume the editorial office will address this for correctness on a later stage.
Reply b): We aligned the affiliation section according to the comment. (See Page 1)

(c) Abstract – Under the Method section – line 35 – please consider writing “minimally invasive percutaneous procedure kit (MIPP kit PNX)” and what PNX stand for.
In the results section of the abstract – the wording “Three patients (7.5%, 95%
40 CI: 0.0% to 15.7%) had complications after glue injection during PLB”. It appears as if injection of the glue caused the complication (bad). I presume this is not the case. “Out of the 40 patients, 37 had no PLB complication by injecting the glue 37/40 (92.5%) and only 3/40 (7.5%) had PLB complication ” if I am correct. The authors could consider rephrasing the wording.
Reply c): We detailed the acronym of the device in the abstract as suggested (See page 2, line 34 and line 35). Moreover, we reworded the indicated sentence according to the indication of the reviewer (See page 2, line 39)

(d) Introduction – Line 92 consider “31%”, instead “31.0%”
Line 101-102 “for both inflated and deflated lung application” is not very clear. The authors could consider rephrasing the wording.
-line 114- the reference 35 and 36 are represented as superscript, whereas, others are not. I presume the authors might have overlook this from their previous version.
Reply d): We changed the indicated text according to the comments of the reviewer (See page 4, line 92; Page 5, line 102 and Page 5, line 116, respectively).

(e) Methods – Line 135 – although not a big issue but the wording “after informed consent form (ICF) signature” sounds bit odd. It may be better to say “after informed consent (IC)” I think.
Reply: We changed it in the entire text.
I also feel from line 143 -149 where the authors have described the technique, if it could be represented by adding some pictures/figures/illustration, even considering a short video clip will be fantastic.
Reply: A figure showing the device components used to inject a surgical adhesive after CT-guided interventional thoracic procedures was added (see new Figure 1).
Line 151 “Each patient performed 5 study visits” – I think it should read as. “Those patients consented to participate in this study had in a total of five hospital visits during this study period”. That Included a screening/baseline…
Reply: We reworded the sentence (see page 7, line 151).
- Please consider removing the wording “ICF signature” from the entire manuscript. It would be OK to leave it as informed consent “IC”
Reply: We changed it in the entire text.
- Line 158 “clinical examination and imaging tests” – can the authors expand on what specific imaging tests were utilised to assess complication.

Reply: We added the requested information (see page 7, line 158).
- Line 159 – what does “CRFs” mean – could be expanded before abbreviation
Reply: We added information (see page 7, line 160).
- Line 182 – under sub-title – “investigational device”. Please expand “PVC”
Reply: We added information (see page 8, line 182).
- Again in this section some pictorial representation of the device will be good I think.
- Line 191 – it is not clear what the authors are intending to say “administration of the surgical adhesive during diagnostic PLBs”. Are they meaning after the procedure applying the surgical dressing to the procedure site (meaning end of procedure) or something else.
Reply: We mean the administration of BioGlue. Please see the information reported at page 8 (line 181-185).
- Line 192 – again consider just mentioning after IC, instead of ICF signature.
Reply: We changed it in the entire text.
(f) Results – Line 237-238 – I am bit confused hear “Thirty-nine (90.7%) patients of the PB analysis set were hospitalized”. I am not sure what it means, were the patients enrolled into the study were already admitted in the hospital before undergoing the PLB procedure?. If true, bit surprising were most patients for lung cancer/mass diagnosis would be from ambulatory setting.
Reply: The study allowed enrolling patients undergoing PB either as inpatients or as outpatients, according to the investigational sites policies.
Line 278 – should read as “respectively” not “rispectively”
Reply: we changed it (See page 12, line 287).
Under the sub-heading –“Evaluation of MIPP-Kit PNX impact on investigational site costs”. It is not clear how many patients required hospitalisation post procedure.
- It would be interesting to include the biopsy yield (diagnosis) with this technique/ procedure. Can the authors consider including this data in the results.
No outpatients undergoing PB required hospitalization, while inpatients with complications required a prolongation of it (See page 13, line 299-305).

We have not captured the biopsy yield information in the CRF, given the intended use of the device and the objective of the trial.

(g) Discussion – Satisfactory and relevant
(h) Conclusion – line 368 – should read as “support” not “suport”
Reply: we changed it (See page 16, line 386).
(i) Acknowledgments: Not clear why the authors are repeating the Ethical statement under acknowledgment again, that has already been mentioned in the method section. If not required can be considered to be deleted or move to the method section to represent it in more in detail, but not to be repeated. Until and unless the authors intentions are to please the ethics committee in the acknowledgment section, that could be worded as – we thank the ethics committee for …..
Again – I also think that the conflict of “of” please remove the extra “of” and also the entire of, as I think this should not be represented in the acknowledgment section in my opinion.
Reply: the section adds information regarding the number of the approving document at each

EC involved.
(j) Tables – Nil issues noted
(k) Figures: Nil Issues noted
(l) Ethical approval: Satisfactory
(m) References: not checked – authors to make sure that the references are accurate and appropriate

Reviewer D

In this article, the authors investigated the feasibility and safety of the device to prevent complications such as pneumothorax, hemoperitoneum, and air embolism, etc., and concluded the device is safe and effective. However, this study is related to some limitations and issues as follows.

#1 The number of enrolled procedures is too small to prove their safety and effectiveness. Additionally, single-arm seems to be inappropriate for this purpose. Three minor complications are found after glue injection, but it is unclear if these complications happened without glue injection. Comparison between with and without MIPP-Kit PNX evaluating a larger number of patients is ideal.
Reply 1: As a first-in-human study, this clinical investigation was designed as an hypothesis-generating study (see the entire discussion section).

#2 The pre-and post-glue complications are analyzed separately but it looks unfair to compare the rate of complication in the previous reports with the only post-glue complication (pneumothorax and pulmonary hemorrhage).
Reply 2: Considering the intended of use of the device, the study objective and design, as well as the mechanism of action of the MIPP-Kit PNX, this analysis is useful to collect information on any device administration-related adverse events (including any complications of the procedure); however, both pre- and post-glue administration AEs were analyzed, for the sake of completeness (see page 15, line 357-361).

#3 The last paragraph states the purpose of this study is to assess the safety and feasibility whereas the authors mention effectiveness in the conclusion. The purpose needs to correspond to the conclusion.
Reply 3: Considering the intended of use of the device and the mechanism of action of the MIPP-Kit PNX, its performance information (i.e., efficacy) is strictly related with its safety/feasibility data, and specifically with the recording of any treatment-emergent adverse events.

#4 How the dose of BioGlue was determined? Does it depend on the length of the track?
Reply 4: Length of the track, depth of the lesion, outer caliber of the introducer and clinical judgement; we added more clarification on this in the “Methods/Investigational device” section. (See page 8, line 208-211).

#5 The secondary endpoint is addressed in the statistical analysis but it needs to be defined in the former part of the materials and methods.
Reply 5: The secondary endpoints are also described in the “Outcomes” section (Page 9, line 208-212).

#6 Only widely accepted abbreviations (e.g., CT, IQR, CI, etc.) can be used in the manuscript.
Reply 6: We reported for each acronym its spelled out meaning the first time it was used in the text of the manuscript.

#7 It is recommended to show the picture and/or figure to explain the device.
Reply 7: We added a figure of the MIPP-Kit PNX components used to inject the surgical adhesive after CT-guided interventional thoracic procedures (see new Figure 1)