

## Safety and efficacy of tuberculin skin testing with microneedle MicronJet600™ in healthy adults

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### SUMMARY

**SETTING:** Intradermal injection using a syringe and needle is generally accepted as the most accurate method for the tuberculin skin test (TST). However, the Mantoux technique using a conventional needle is often difficult to perform reliably, affecting testing results and safety.

**OBJECTIVE:** We evaluated the efficacy and safety of a novel intradermal injection device, the MicronJet600™ microneedle, compared with conventional injection in terms of skin reactivity to the TST.

**DESIGN:** A prospective, open-label clinical study was conducted. The TST was administered by both methods in the same subject. For pain assessment, participants filled in a visual analogue scale (VAS) after each TST. Any side effects due to TST or injections were observed.

**RESULTS:** TST reaction rates (cut-off  $\geq 5$  mm) from microneedles and needles were respectively 44.0% and 47.2%, with no significant difference between the two. Furthermore, agreement of positivity between the two methods was excellent with both 5 mm and 10 mm cut-off values. However, the level of pain experienced when microneedles were used for TST was significantly lower than with conventional needles. No adverse effects were attributed to the MicronJet device.

**CONCLUSION:** The novel microneedle device used for TST in this study was effective, safe and less painful in healthy adult volunteers.

**KEY WORDS:** microneedle device; TST; Mantoux; intradermal

TUBERCULOSIS (TB) REMAINS a major public health problem in the world. It is known that one third of the world's population has latent tuberculous infection (LTBI); these individuals have been infected with *Mycobacterium tuberculosis*, but have not yet clinically developed the disease.<sup>1</sup> Accurate diagnosis of LTBI, followed by proper chemoprophylaxis, might be an effective way to control TB and prevent it from spreading within a high-risk population.

The tuberculin skin test (TST) is widely used for the diagnosis of LTBI. Intradermal injection using a syringe and needle, called the Mantoux technique, is generally accepted as the most appropriate method for the TST, as the delivered purified protein derivative (PPD) dose (0.1 ml) can be precisely measured and controlled, resulting in more consistent mycobacteria-specific immunity.<sup>2–5</sup> However, it requires a well-trained nurse who is skilful with the

technique in the field to form a wheal with an acceptable size of  $>6$  mm in diameter, indicating proper intradermal injection of PPD into the epidermal layers of the skin.<sup>6</sup> The percutaneous method, using a multipuncture device, has also been introduced to overcome issues such as mass, and to facilitate the rapid and less skillful administration of the TST.<sup>7</sup>

A novel microneedle device for intradermal injection has recently been introduced to complement an unmet need in the intradermal delivery of vaccines and other biologics.<sup>8</sup> The MicronJet600™ (Nano-Pass Technologies Ltd, Nes Ziona, Israel) used in this study is composed of three microneedles, 0.6 mm in length, enabling controlled delivery depths with minimal pain and lowered risk associated with handling needles during injection. The device is designed to be mounted on any standard syringe

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and used as a substitute for a conventional needle in intradermal injection.<sup>9</sup> Previous studies have shown that various types of vaccines, such as the seasonal and pandemic influenza vaccines, can be delivered via the intradermal route with favourable efficacy and safety, compared with intramuscular injection.<sup>8,10–14</sup> In addition, MicronJet can be used for other drugs or vaccines currently delivered by intradermal injection, such as insulin, rabies, influenza and anthrax, to control injection depth, reduce injection pain and ease the need for skilled users.<sup>15</sup>

We conducted a study to evaluate the performance of a novel microneedle device in the intradermal injection of PPD in healthy volunteers. The aim of the study was to compare the results of TST administered using a conventional syringe and needle method and the MicronJet method, in terms of efficacy and safety.

## STUDY POPULATION AND METHODS

### *Study design and participants*

This was a randomised, open-label study to evaluate the efficacy and safety of the novel MicronJet microneedle device for applying the TST in healthy adults. Healthy volunteers aged 20–60 years were recruited at a tertiary hospital, the Severance Hospital, Seoul, Republic of Korea, from November 2014 to March 2015. All participants were screened using chest X-ray (CXR), and clinical information, including history of BCG vaccination, TB, TST and other comorbidities, was collected onto clinical research forms on interview. Individuals with an abnormal CXR or any chronic illness with immune suppression, such as uncontrolled diabetic condition, chronic liver disease, taking immunosuppressive agents, or history of TB or TST, were excluded. After enrolment, a trained nurse administered the TST twice for each subject on both the left and the right arms, starting with either the conventional needle or the microneedle. The site of PPD injection using the microneedle device was assigned by block randomisation.

Approval for the clinical study using an investigational medical device was provided by the Korean Ministry of Food and Drug Safety, Seoul (Study No. 644). Ethical approval was provided by the Institutional Research Board of Severance Hospital, Seoul, Republic of Korea (IRB #1-2014-0026). All volunteers provided written informed consent to participate in the study.

### *Tuberculin skin test with a microneedle device and a conventional needle*

For each TST, 0.1 ml of 2 tuberculin units of tuberculin PPD RT23 (Statens Serum Institut, Copenhagen, Denmark) was administered on one arm with a microneedle device and the other arm with a conventional needle in the same subject by a trained nurse. The MicronJet devices were donated

by NanoPass Technologies Ltd, and were used according to the manufacturer's instructions. To assess the proper intradermal injection with 0.1 ml of PPD, the size of the white vesicle (wheal) of each injection site was measured in mm. For pain assessment, a Visual Analogue Scale (VAS) pain score graded 0 from 10 was recorded after each PPD injection. After 48–72 h, the induration diameter transverse to the long axis of the arm was measured by two trained nurses. Any side effects due to TST or injections were observed before the skin reactions were read.

### *Determination of the number of participants*

The sample size of the study was determined by the following factors: the previously reported rate of TST reaction ( $\geq 5$  mm) in Korean adults,<sup>16,17</sup> significance level and power, and equivalence margin difference in rates of TST reaction between the two methods (conventional needle and microneedle). Using an equivalence test for two correlated rates and assuming a value of 40% for the TST reaction ( $\geq 5$  mm) with a significance level of 0.05, a power of 0.80 and an equivalence difference of 10%, the minimum sample size was estimated to be 152.<sup>15</sup>

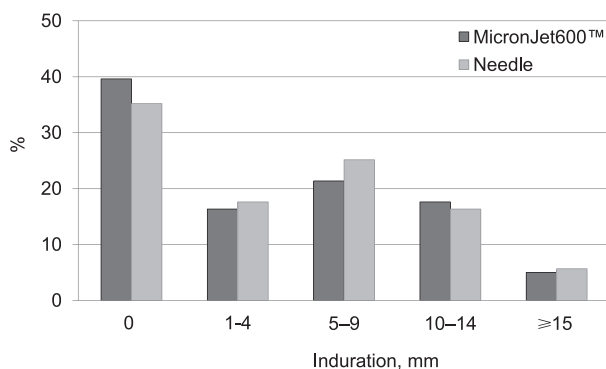
### *Statistical analysis*

Data analyses were performed using SAS 9.3 software (Statistical Analysis System, Cary, NC, USA). To compare the TST indurations, VAS scores and wheal sizes from the two methods of PPD administration in each study subject, the paired *t*-test was used. Comparison of the rates of TST reaction between the two methods was performed using the McNemar test. Relationships between the two methods were analysed using  $\kappa$  statistics and Pearson correlation coefficient. In the  $\kappa$  statistics,  $\kappa > 0.75$  represented excellent agreement beyond chance, while  $\kappa 0.4$ – $0.75$  represented fair to good agreement beyond chance. Comparison of the primary outcome, i.e., rates of TST reaction, between the two PPD administration methods were evaluated with the lower boundary and upper boundary of one-sided 95% confidence intervals (CIs) using an SAS macro suggested by Tango based on the score method.<sup>18,19</sup>  $P < 0.05$  was seen as significant.

## RESULTS

### *Characteristics of participants*

A total of 159 participants were enrolled in the study. There were no losses to follow-up or dropouts during the study. Of 159 participants, 63 (39.6%) were male and 96 (60.4%) female; the mean age was 34.5 years (range 20–59). From the BCG scar inspection at the site, 145 (84.3%) participants still had BCG scars on the left upper arm. The mean body mass index (BMI) was  $23.3 \pm$  standard deviation (SD) 3.2 kg/m<sup>2</sup>; 8



**Figure** Distribution of TST indurations with MicronJet600™ and the conventional injection needle ( $n=159$ ). TST = tuberculin skin test.

(5.0%) participants said that they had had contact with TB patients in the past.

### Efficacy

In terms of skin reactivity, we evaluated the efficacy of TST using MicronJet devices compared with conventional needles in 159 participants (Figure). TST reaction positivity (cut-off  $\geq 5$  mm) from the two methods of administration was 44.0% with MicronJet and 47.2% with the needle. Similarly, the TST positivity rates (cut-off  $\geq 10$  mm) were 22.6% with MicronJet and 22.0% with the needle. The TST reaction with MicronJet was equivalent to that seen with the conventional needle, as the lower and upper boundary of differences measured were within the pre-defined equivalence margin of 10% (Table 1).

The mean induration sizes of the TST reaction, after excluding non-reactors (induration 0 mm in both groups), were  $7.2 \pm 5.4$  mm with MicronJet and  $7.5 \pm 4.9$  mm with the needle; there was no significant difference between the two methods ( $n=110$ ,  $P=0.062$ ). However, the difference in mean indurations of MicronJet and the needle approached significance, mainly affected by two outliers with respectively 0–5 mm and 0–8 mm in paired induration sizes of the MicronJet and the needle method.

When plotting the results of the TST with MicronJet and the needle, paired TST indurations performed by two methods of administration in the same subject were well correlated (correlation coefficient = 0.970,  $P=0.0001$ ). Agreement of TST positivity between the MicronJet and the needle methods was excellent at

**Table 1** Effect of TST method on positive reaction rate

TST positivity cut-off	MicronJet600™ %	Needle %	Difference % (95%CI)*
5 mm	44.0	47.2	–3.2 (–6.6 to –0.5)
10 mm	22.6	22.0	0.6 (–2.1 to 3.5)

\* One-tailed.

TST = tuberculin skin test; CI = confidence interval.

**Table 2** Agreement of TST-positive reaction rates between MicronJet and the needle methods

MicronJet600™	Needle $n$		Agreement $\kappa$
Cut-off	<5 mm	$\geq 5$ mm	Total
<5 mm	83	6	89
$\geq 5$ mm	1	69	70
Total	84	75	159
Cut-off	<10 mm	$\geq 10$ mm	Total
<10 mm	121	2	123
$\geq 10$ mm	3	33	36
Total	124	35	159

TST = tuberculin skin test.

both 5 mm and 10 mm cut-offs (respectively  $\kappa = 0.911$  and  $\kappa = 0.909$ ) (Table 2). Using a 10 mm cut-off, two participants showed 13 and 12 mm indurations with the needle but 9.5 and 7.5 mm with MicronJet, while three participants showed 10, 10 and 12 mm with MicronJet, but 9, 8.5 and 9.5 mm with the needle, respectively.

### Safety

During TST administration in 159 healthy volunteers, one mild adverse skin reaction with redness, itchiness and a blister that burst at the injection site was observed due to TST reactivity itself. However, no adverse events or safety concerns were attributed to the microneedle device or conventional needle. No breakage of microneedles was reported during the study. There were no reports of any other mechanical failures.

### Usability

We evaluated the utility of the novel microneedle for PPD injection for both participants and study nurses. For study participants, we measured the relative degree of pain following injections with both microneedles and conventional needles. Among the 159 participants, the mean VAS pain score was  $3.4 \pm 1.7$  with MicronJet and  $4.9 \pm 1.9$  with the needle, showing that pain scores with MicronJet were significantly lower than with the other method ( $P < 0.001$ ) (Table 3).

In addition, we measured the size of the wheals formed after each injection of 0.1 ml PPD; the wheals should be  $>6$  mm in diameter when successful. In this study, all injections achieved the proper wheal size (100%) according to current national guidelines. However, microneedles yielded larger wheals than did conventional needles ( $P < 0.0001$ ; mean 8.52 vs. 7.67 mm).

## DISCUSSION

In this study, we found that there were no significant differences in TST reaction rates at 5 mm and 10 mm cut-off between microneedles and conventional needles.

**Table 3** Comparison of VAS pain scores

VAS pain	MicronJet600™	Needle	Difference*	t-statistics	P value*
Mean $\pm$ SD	3.4 $\pm$ 1.7	4.9 $\pm$ 1.9	-1.4 $\pm$ 1.8	-9.86	<0.001
Median (min-max)	3 (0-9)	5 (1-10)	—	—	—

\* The difference in scores was calculated by subtracting the VAS pain score for the MicronJet method from that for the needle method for each subject.

VAS = Visual Analogue Scale; SD = standard deviation.

dles. The difference in induration associated with the use of the two methods was not statistically significant, and correlations between the TST inductions performed by the two methods in the same subject were excellent. In addition, no adverse events or safety concerns were attributed to microneedle devices, with low pain response in participants and acceptable usability in study nurses.

The TST and the interferon-gamma release assay (IGRA) are currently used to diagnose LTBI worldwide. Improvement of PPD delivery by the Mantoux technique is important to TB control programmes for LTBI screening in contact investigations, among hospital employees and in national surveys. Where nurses do not have training in TST application, leakage of PPD solution at the injection site might occur, necessitating repeated skin tests.<sup>20</sup> Based on our results, the 0.6 mm microneedle device allows intradermal administration with minimal expertise for the nurses who apply the TST injections and minimal pain for the recipients, and shows valuable advantages over conventional needles, including reduced need for training and less needle fear, stress and discomfort associated with intradermal injections. In addition, the use of a microneedle device helps reduce any risks or injuries associated with the handling of used needles at the field site, particularly in a school setting.

To compare TST results between the two methods in our study, two trained nurses independently measured the indurations of the skin reaction, and were blinded to the injection method on each arm. Although there were two or three notable differences in readings, most were well correlated between two nurses (Spearman rank correlation = 0.96 with MicronJet, 0.95 with the needle); we thus averaged readings from the two nurses for each of the methods. One of the key factors for the interpretation of TST reading variability can be intra- and inter-observer consistency between different readers, which should be controlled and minimised by training.<sup>21-23</sup> With respect to the unavoidable reading variations in the TST, the small differences in TST results between the MicronJet and the needle methods in our study could be acceptable in the field.

Regarding pain assessment in this study, participants marked lower pain scores for TST using microneedles compared to conventional needles, but the difference in score (-1.4) was not as large as

expected, although it was significant. This might be because our study participants were adults aged 20-60 years (mean age 34.5); this age group tends to have less needle fear than children or young adults.<sup>24</sup> The difference in pain scores might have been greater if we had performed the TST in children or young adults. Taking into consideration the greater needle fear in children and young adults, we expect that the microneedle device, MicronJet may be feasible for contact investigation that occurs mainly in schools.

By introducing microneedle-based delivery of PPD, specific hurdles of the TST related to injection skills, safety, and pain due to conventional needles may be overcome. However, the limitations of the TST itself, due to possible errors made by examiners, previous BCG vaccination or infection with non-tuberculous mycobacteria, remain unresolved. Although the agreement of TST reactivity between microneedles and needles was excellent in our study, we noted several participants with different sizes of induration near the 10-mm cut-off, which might affect the determination of LTBI diagnosis in the field. This suggests that without improved skills for the measurement of induration ('by definition') and the interpretation of tests in different populations, despite administration using microneedles, the TST still has limitations in the diagnosis of LTBI.

The usefulness of this microneedle-based device is not restricted to the TST. It may be extended to BCG vaccination (or novel TB vaccination with intradermal delivery) and any drug deliveries requiring intradermal injection, as shown in recent studies.<sup>10-14</sup> Unlike percutaneous administration by other multipuncture devices for the BCG vaccination, if validated by a clinical study, MicronJet may deliver the BCG vaccine (or novel TB vaccines) by intradermal administration, by which the delivered dose can be precisely measured and administration can be controlled, resulting in improved mycobacteria-specific immunity.<sup>2,25,26</sup>

## CONCLUSION

In this study, we found that the use of microneedle devices did not negatively affect the result of the TST, and that an acceptable amount of PPD was administered to the Mantoux recipient with less pain compared with that of conventional needles. In addition, no adverse events or safety concerns were



attributed to the microneedle device. Overall, among 159 healthy participants, the TST using microneedles was as effective and safe as a conventional needle. The use of a novel microneedle device can therefore be expanded to the TST.

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Conflicts of interest: none declared.

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**RESUME**

**CONTEXTE :** Une injection intradermique à l'aide d'une seringue et d'une aiguille est généralement acceptée comme la méthode la plus précise pour effectuer le test cutané à la tuberculine (TST). Cependant, la technique de Mantoux, qui recourt à une aiguille conventionnelle, est souvent difficile à réaliser de manière fiable, ce qui affecte à la fois les résultats du test et sa sécurité.

**OBJECTIF :** Nous avons évalué l'efficacité et la sécurité d'une nouvelle technique d'injection intradermique à l'aide d'une microaiguille (MicronJet600™) comparée à l'injection conventionnelle, en termes de réactivité cutanée au TST.

**SCHEMA :** Une étude clinique ouverte prospective a été réalisée. Les TST ont été faits selon les deux méthodes sur le même sujet. Les participants ont rempli une échelle analogue visuelle (VAS) après chaque TST afin d'évaluer

la douleur provoquée. Tout effet secondaire dû au TST ou aux injections a été observé.

**RÉSULTATS :** Les taux de réaction au TST (seuil  $\geq 5$  mm) dus aux microaiguilles et aux aiguilles ont été respectivement de 44,0% et 47,2%, sans différence significative entre les deux. De plus, l'accord de positivité entre les deux méthodes a été excellent avec des valeurs de seuil d'à la fois 5 mm et 10 mm. Cependant, le niveau de douleur ressenti avec l'utilisation des microaiguilles a été significativement plus faible qu'avec les aiguilles conventionnelles. Aucun effet secondaire n'a été attribué au MicronJet.

**CONCLUSION :** La nouvelle microaiguille utilisée pour le TST dans cette étude s'est avérée efficace, sûre et moins douloureuse chez des adultes sains volontaires.

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**RESUMEN**

**MARCO DE REFERENCIA:** En general, se acepta que el método más preciso de practicar la prueba tuberculínica (TST) es una inyección intradérmica utilizando una jeringuilla con aguja. Sin embargo, la técnica clásica de Mantoux con una aguja corriente suele ser difícil de llevar a cabo de manera fiable, lo cual altera los resultados TST y modifica su seguridad.

**OBJECTIVO:** Evaluar la eficacia y la inocuidad de un nuevo tipo de inyección intradérmica, utilizando una microaguja (MicronJet600™) y comparar con la inyección clásica, con respecto a la reactividad cutánea a la TST.

**MÉTODOS:** Fue este un estudio clínico prospectivo sin enmascaramiento. Se practicó a cada persona la prueba TST mediante dos métodos. Los participantes completaron una escala analógica visual (VAS) con el fin de evaluar el dolor después de cada prueba. No se

observaron reacciones adversas debidas a la tuberculina ni a las inyecciones.

**RESULTADOS:** La tasa de reacción TST con la microaguja fue 44,0% y con las agujas clásicas fue 47,2% (induración discriminatoria  $\geq 5$  mm), una diferencia sin significación estadística. Además, la concordancia de la positividad de la reacción fue excelente con ambos umbrales discriminatorios (5 mm y 10 mm). Sin embargo, el grado VAS de dolor referido fue significativamente inferior cuando se usaron microagujas en comparación con las agujas clásicas. No se atribuyeron reacciones adversas a la utilización del dispositivo MicronJet.

**CONCLUSIÓN:** En el presente estudio, la utilización del nuevo dispositivo con microaguja en la prueba TST fue eficaz, segura y menos dolorosa en los adultos sanos voluntarios que participaron.

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