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THE FUNCTIONAL AND HISTOLOGIC CHANGES ELICITED BY SUBURETHRAL PROLENE MESH IN THE MOUSE MODEL WITH SIMULATED BIRTH TRAUMA INDUCED STRESS URINARY INCONTINENCE

Hypothesis / aims of study

Using synthetic slings or meshes to treat stress urinary incontinence (SUI) or pelvic organ prolapse has been gaining its popularity for a while. However, long term follow-up had not been available to address clinical concerns related to delayed or perioperative complications including mesh erosion/exposure [1], voiding dysfunction, de novo urgency over time. Thus, an available animal model is necessary for studying those untoward events. In this study, we aimed to examine the functional and histologic changes elicited by the prolene mesh under the mice urethra after vaginal distension (VD) and sought to create a novel animal model for testing the possible mechanisms of induced above mentioned complications.

Study design, materials and methods

We have recently reported successful induction of SUI in mice by VD [2]. We distributed 36 virgin female C57BL/6 strain mice into 3 groups. Under isoflurane anesthesia, 2 groups underwent VD and 1 group of them also received prolene mesh implant therapy. The third group was as control. On our pilot experiments, in which we found no significant differences in cystometric parameters between the mice treated after VD + sham mesh implantation and VD (data is not shown, due to space limitation). Mice in the sham VD group were anesthetized and subjected to the vaginal wall incision and repaired by 7-0 silk, without placement of the mesh. Each group was divided into 2 subgroups for the conscious cystometrogram (CMG), leak-point pressure (LPP) testing at 4 and 10 days, respectively after VD. After sacrifice, the urethras and the vaginas of the mice were harvested for histological examination and matrix metalloproteinase (MMP)/ tissue inhibitors of metalloproteinase (TIMP) staining. Comparisons of the urodynamic results among groups at the same time point were performed. The differences among groups and pairwise comparisons were evaluated by Kruskal-Wallis and Wilcoxon rank sum test, respectively,with $p<0.05$ indicating a significant difference.

Results

There was no significant difference among those groups in peak voiding pressure, either at day 4 or 10 ($p=0.069$, $p=0.890$, respectively). However, LPPs in VD + mesh group were significantly higher than the other 2 groups both at day 4 and 10 ($p<0.001$, $p<0.001$, respectively). Moreover, voided volume and voiding interval in VD+ mesh group are higher than the other 2 groups only at day 4 ($p<0.001$, $p=0.004$, respectively), (Table 1, 2). Histological examinations showed MMP/TIMP expression increased in the suburethral area 4 days after vaginal dilation in VD + mesh group. [Fig. 1]

Interpretation of results

As we know, the mechanism to achieve continence in midurethral sling is dynamic kinking of the urethra. On experiment, we were able to create the mice modes with their urethras kinked by gentle pressure with a finger applying to their abdomens during the measurement of LPP. Significantly increased LPPs were noted in VD+ mesh group both at day 4 and 10. This might be due to a sturdy continent effect caused by local tissue remodeling in the urethra. The reason for the voding pressure being not significantly changed among 3 groups both at day 4 and 10 was because of the mesh being placed under no tension. After sacrifice, histological examinations showed increased MMP/TIMP expression in the suburethra 4 days after vaginal dilation in VD +mesh group indicating tissue remodeling possibly being related to the mesh placement. Changing the expression of MMP/TIMP might be due to tissue remodeling caused by the mesh, while the tissue remodeling might be related to alterant tissue pressure, ischemic change, or inflammatory response…etc.The limitation of this animal model is that the mouse is tetrapod and the pelvic floor structure is different from that of human beings. Therefore, results of this study should be carefully applied to human subjects.

Concluding message

Based on this newly created mice model, if proteinases in tissue remodeling can be controlled in our future mechanistic studies, we might be able to prevent mesh erosion or other complications alike.

Table 1 Day 4

	Control (n=6)	VD (n=6)	VD+ mesh tape (n=6)	P-value
Voiding pressure (cm H2O)	10.27 ± 2.67 9.8 (7.3, 13.9)	12.78 ± 1.75 12.65 (10.6, 15.8)	14.6 ± 2.74 15.2 (10.3, 17.9)	0.069[a]
Voided Volume (μL)	43.33 ±7.00 41 (37, 53)	66 ± 11.98 63.5 (52, 84)	86.67 ± 15.56 92.5 (62, 104)	<0.001[a] 0.004(i) 0.002(ii) 0.045(iii)
Voiding Interval (seconds)	121.9 ± 20.42 116.60 (100.2, 150.2)	167.73 ± 10.60 168.28 (153.6, 180.5)	174.18 ± 36.03 183.03 (107.1, 204.1)	0.004[a] 0.002(i) 0.026(ii) 0.310(iii)
LPP	21.9 ± 2.34	4.63 ± 2.04	30 ± 0	<0.001[a]

(cm H2O)	21.90 (19.3, 25.1)	4.45 (2.2, 7.4)	30 (30, 30)	0.002(i) 0.002(ii) 0.002(iii)

Table 2 Day 10

	Control (n=6)	VD (n=6)	VD+mesh tape (n=6)	P-value
Voiding pressure (cm H2O)	11.23 ± 1.81 10.65 (9.5, 14.2)	12.08 ± 2.96 11.75 (9.3, 17.5)	11.55 ±1.84 10.96 (9.7, 15.0)	0.890[a]
Voided Volume (μL)	69.67 ±13.46 68.5 (55, 88)	54 ± 24.26 52 (22, 83)	40 ± 16.35 38 (23, 67)	0.052[a]
Voiding Interval (seconds)	148.83 ± 19.88 153.6 (120.5, 170.2)	165.80 ± 65.23 143.15 (109.25, 276.30)	120.19 ± 25.47 115.13 (89.25, 162.40)	0.139[a]
LPP (cm H2O)	22.2 ± 2.46 22.9 (18.7, 24.8)	19.3 ± 3.57 19.15 (15.1, 24.5)	30 ± 0 30 (30, 30)	<0.001[a] 0.180(i) 0.002(ii) 0.002(iii)

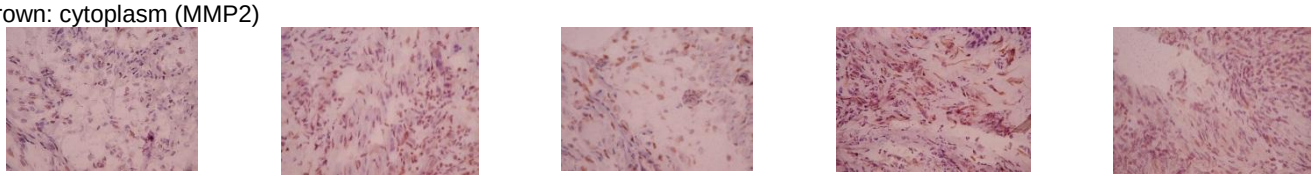
Data are presented as mean± SD and median (minimum, maximum)

a: The p-value represents the significance among 3 groups using Kruskal-Wallis test. If the overall differences exist, the significance from three pairwise comparisons using Wilcoxon rank sum test then follow: (i) between control and VD groups, (ii) between control and VD+mesh tape groups, and (iii) between VD and VD+mesh tape groups, respectively.

● 400 X

Blue: cell nuclei (Hematoxylin)

Brown: cytoplasm (MMP2)



Control VD-4D VD-10D VD+mesh-4D VD+mesh-10D

Figure 1.

References

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Disclosures

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