EXTRACORPOREAL SHOCK-WAVE THERAPY IMPROVES MOTOR DYSFUNCTION AND PAIN ORIGINATING FROM KNEE OSTEOARTHRITIS IN RATS

[Introduction]
Extracorporeal shock-wave therapy (ESWT) is currently used to treat painful orthopedic disorders. There have been several reports on the use of extracorporeal shock waves in the treatment of pseudarthrosis, calcifying tendinitis, and tendinopathies of the elbow. However, the efficacy of ESWT for knee osteoarthritis (OA) has not been established.

[Purpose]
To investigate the effect of shock wave application for knee OA, we analyzed walking duration on a treadmill and changes of calcitonin gene-related peptide (CGRP), which is a marker of inflammatory pain, and growth-associated phosphoprotein (GAP-43), which is used as a marker of nerve regeneration in dorsal root ganglion (DRG) neurons of OA rats using immunohistochemistry.

[Materials and Methods]
The experimental protocol was conducted in accordance with the guidelines of the Ethics Review Committee of Chiba University for Animal Experimentation.

OA model: We transected the anterior cruciate ligament, medial meniscus and medial collateral ligament to make an OA model, and evaluated 18 knee OA rats 6 months after the surgery.

Behavioral test: Six knee OA model rats were used for behavioral analysis. We measured walking duration before application of shock waves, and then 2 days, 4 days, 7 days, 14 days, 21 days and 28 days after shock wave application. Changes in distances were statistically significant as evaluated by non-paired t-test.

Immunohistochemistry: We used 3 groups. 1) control group (6 knees); 2) knee OA group (6 knees); and 3) knee OA + shock wave group (6 knees). Fluorogold (FG a neurotracer: 100 µl (10% saline with FG)) was applied to the medial knee joint 10 days after injection of FG. All rats were perfused 14 days after application of FG. After fixation, DRGs from L1 to S1 were harvested, sectioned, and immunostained for CGRP and GAP-43. 1) The number of FG-labeled neurons; 2) the ratios of CGRP-immunoreactive (ir)+FG-labeled neurons/ FG-labeled neurons; 3) the ratios of GAP-43-ir+FG-labeled neurons/ FG-labeled neurons; and 4) the ratios of triple-ir neurons/ FG-labeled neurons were compared statistically among three groups using the Mann-Whitney U-test.

[Results]
Behavioral test: Walking duration in OA model rats was significantly shorter than in control rats. However, walking duration on a treadmill was significantly extended 2 days, 4 days, 7 days and 14 days after application of shock waves in OA rats (p<0.05). However, there was no significant difference in walking duration on days 21 and 28 compared with duration before shock wave application (Fig.1). Shock wave therapy was effective for approximately 14 days.

Immunohistochemistry: (Fig.2 & Fig.3)
1) FG-labeled neurons: In the 3 groups, FG-labeled DRG neurons innervating the medial knee joint were distributed from L2 to L6. There was no significant difference in distribution between the groups.
2) CGRP-ir neurons: Of FG-labeled neurons, the ratios of CGRP-ir neurons in the control and shock wave groups were significantly smaller than in the OA group (control group (48.3%); knee OA group (87.0%); shock wave group (49.8%)) (p<0.05). Shock wave application reduced the ratio of CGRP-ir neurons in the DRG of OA model rats.
3) GAP-43-ir neurons: Of FG-labeled neurons, the ratios of GAP-43-ir neurons in the control and shock wave groups were significantly smaller than in the OA group (control group (14.6%); knee OA group (65.1%); shock wave group (14.3%)) (p<0.05). Shock wave application reduced the ratio of GAP-43-ir neurons in the DRG of OA model rats.

[Discussion and Conclusion]
Our results demonstrate that the percentage of neurons expressing GAP-43 in the knee OA group was significantly higher than in the control group. Since GAP-43 is highly expressed during axonal growth and regeneration, this result suggests that inflammation of the knee joint potentially promotes knee afferents to extend their axons into the affected knee. The proportion of GAP-43-ir knee afferents that were CGRP-positive was increased in the OA group. This suggests that small nociceptive DRG neurons are more likely to extend their axons into the knee and cause knee pain.

We previously reported that application of shock waves to normal rat skin reduced both CGRP expression in DRG neurons and degeneration of free nerve endings. Shock waves were applied to a pathological model in the current study, and we confirmed the reduction of CGRP-ir neurons and CGRP-ir, GAP-43 double-immunostained neurons in the DRG, and observed improvement in running ability. These data show that ESWT may be useful for the treatment of knee OA.

** Div. of Orthopedic Surgery, Chiba Children’s Hospital, Japan
***Dept. of Orthopedic Surgery, Teikyo University Ichihara Hospital, Japan

E-mail address: nobunobu1215@yahoo.co.jp

+*Dept. of Orthopedic Surgery, Graduate School of Medicine, Chiba University, Japan

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