DISCUSSION

Although there are several lines of evidence from many controlled and uncontrolled studies for the short-term and long-term effectiveness of acupuncture in relieving clinical pain [43-46,78-79], the scientific data concerning the efficacy of acupuncture in OA are rare [28]. In addition, there are several systemic flaws among these studies due to inadequate statistical power [44-46,78], inadequate number of acupuncture treatments [78], failure to control for concomitant therapies [44], and no sham or placebo acupuncture controlled group [44,79]. In this study, we minimized the methodological limitations of previous studies by using the randomized, single-blind, placebo controlled design with larger sample size of OA patients and coupled with using standard outcome assessments. By using the percentage of the responders as the main efficacy criteria [47], comparison between true and sham acupuncture needs at least 61 patients per group, whereas only 35 patients per group are needed to compare between true and placebo acupuncture performed by avoiding inserting needle through the skin [43]. In order to increase the ability of differentiating true apart from placebo effects and to minimize the sample size, we thus selected the procedure performed by attaching the acupuncture points with the patch electrodes as placebo EA and at least 45 completers per group were treated in this trial. In this study, a double-blind design was considered not appropriate since we used patch electrodes as placebo EA and our patients might recognize the difference between true and placebo EA, a single blind was therefore the reasonable alternative. The acupuncture points used were selected because we intended to determine only the effects of acupuncture points which locate around the affected knee, especially the medial aspect which related to the knee compartment frequently involved in OA. The points selected here were therefore different from other trials [44,79] which also included the distal points at medial and lateral aspects of leg. The biphasic pulses (negative followed by positive or vice versa) was selected to stimulate acupuncture points in order to reduce electrolysis induced by using either positive or negative pulses alone [47].

In this study, the clinical responses observed in placebo group might be the results from: 1) the placebo effect or the natural fluctuations in the symptoms of OA unrelated

to analgesic effect of paracetamol, because some patients demonstrated reductions in these scores without or with minimal analgesic need, or 2) the direct effects of paracetamol as rescue analgesic. The latter reason made the placebo group not absolutely inert to be the control group because paracetamol is also the first-line drug in treatment of OA of knee. However, the use of rescue analgesic could not be avoided due to ethic reasons. The insignificant changes in paracetamol consumption among the four groups during treatments might be the results from: 1) unnecessary use of paracetamol in the great majorities of active treatment groups, because there were no changes in paracetamol consumption among the groups despite significant reductions in various scores in EA and combined groups and a tendency of reductions in diclofenac group, or 2) the high variation of mean changes in paracetamol consumption in each group contributed to the false negative result due to inadequacy of power of test.

The study of short-term efficacy of NSAIDs in treatment of OA demonstrates 10 to 20% differences between base-line and post-treatment scores, with typical base-line VAS values of 40-60 (on a scale of 0 to 100) and post-treatment values of 25-45 [80]. In our present trial, the decreases in mean and median values of VAS in diclofenac group were approximately 50 and 60%, respectively. These reductions were greater than the values mentioned above and might be due to the additive effects from placebo EA. However, there were no significant differences in the median values of VAS, WOMAC scores and Lequense's index between placebo and diclofenac groups. These might be the results from: 1) the equivalent amount of paracetamol consumption in both groups, which suggest that paracetamol alone may be effective to relieve OA symptom, and the concomitant use of diclofenac may not enhance the effectiveness further, or 2) the sample size may be inadequate to demonstrate the differences in mean or median values between the groups because the calculation of sample size in this study was based on using response rates as the major criterion. However, the consistently greater but insignificant reductions in most values of diclofenac group lend support to the latter possibility.

At week 4, the greatest improvement in all variables was demonstrated in EA group. These data indicate the great potential of EA in symptomatic treatment of OA of knee. This study also demonstrated that EA was more effective than placebo with respect to VAS and WOMAC stiffness index, and significantly more effective than

diclofenac with respect to VAS. The superiority of EA might be the results from: 1) EA itself was more effective than placebo/diclofenac, or 2) the unnecessary use of paracetamol, the rescue analgesic drug, might enhance the therapeutic effect of EA, but not diclofenac. The recent trial reveals 34 and 14% reductions in the mean values of WOMAC score and Lequense's index, respectively after 4 weeks of acupuncture treatment [79], whereas our study demonstrated 50 and 45% reduction, respectively. These discrepancies might be due to differences in acupuncture points selection, number of points and electrical stimulation technic used, or electrical stimulation parameters. The clinical responses in combined group were at least equal to diclofenac but not superior to EA groups indicate that EA may exert adequate analgesic effect which may not be benefited further by combination with diclofenac. The failure to demonstrate the differences in other scores or indexes between EA or combined and placebo groups may be due to inadequacy of sample size or the contribution of rescue analgesic used in placebo group (similar to the case of diclofenac group) or both. The insignificant changes in 50 feet-walk time among the four groups suggest that this parameter may not sensitive enough to demonstrate the existing differences, walk time determined during stair climb should thus be a better alternative [81].

The percentage of patients with orthopedist's opinion of "much better" in diclofenac group of this study (36.73%) is consistent with the values of improvement according to physician (approximately 40%) reported in the previous short-term NSAIDs (ibuprofen) trial [14], while the response rates at week 4 in placebo and EA groups are comparable to the success rates previously reported [43,47].

Since the efficacy of diclofenac and EA generally increased by study time, the treatment should thus be continued at least for 4 weeks in order to obtain highest efficacy from either procedure [79]. In this study, the reduction in number of responders during the follow-up period in each group suggests the spontaneous decay in effectiveness after treatment. However, this reduction was more pronounced (although insignificant) in the patients recieving diclofenac (diclofenac and combined groups) than EA and placebo. This may raise question to the abrupt withdrawal of diclofenac after continuous use, taper-off procedure should therefore be considered in diclofenac responders. From routine EA practice, intermitent EA (at least once or twice a month) after the therapeutic period may be helpful to maintain the highest therapeutic efficacy in

EA responders. This study demonstrated that EA treatment was safe and free from serious adverse effects. The indifferences in adverse events between diclofenac and placebo groups regardless of intention to treat analysis or analysis on avialable completers were due to exclusion of patients at risk to adverse effects from NSAIDs during screening visit.

At the end of EA phase of a partial cross-over section in this study, the number of responders as well as the further reductions in the median values of clinical scores and paracetamol consumption confirmed the efficacy of EA and suggest potential use of EA as the alternative treatment in patients with OA of knee regardless of the previous failure to treatment with diclofenac.

In this study, the rescue analgesic paracetamol contributed to several confounding effects. Firstly, it made the placebo group not absolutely inert and not suitable to be control group. Secondly, it necessitated larger sample size to demonstrate the differences in therapeutic outcomes between control and active treatments. Lastly, it confounded the interpretation of the active treatments since paracetamol itself is the first-line drug in OA. Therefore, the randomized placebo controlled trial without using rescue analgesic should be further investigated to confirm the effectiveness of these active treatments, especially EA and its combination with NSAIDs.

The destruction of joint cartilage in OA involves the degradation of matrix molecules, which are released as fragments to synovial fluid, blood and urine where they may be detected. Such cartilage matrix metabolic products could be used as molecular markers to diagnose, prognosticate, and monitor response to therapy in OA. However, the data concerning the effects of specific OA treatment (e.g., NSAIDs) on cartilage markers are rare. In short-term *in vitro* study [82], aspirin reduces proteoglycan and HA synthesis more than the loss of [^{3}H]-HA and [^{3}H]-proteoglycans in explants with moderate and severe OA. In contrast, tenoxicam produces a stronger reduction in the loss of [^{3}H]-proteoglycans than in proteoglycan synthesis, whereas the metabolic balance of HA is minimally affected. In the previous clinical trial [83], the reductions in concentrations and total amount of fragmented proteoglycans (keratan sulphate) in synovial fluid are observed in patients with OA of knee during treatment with piroxicam which are consistent with decreased proteoglycan catabolism. In our study, we determined serum concentrations of cartilage markers instead of synovial fluid

concentrations in order to avoid more invasive and painful procedure of synovial fluid aspiration. However, the indifferences in mean values of serum concentrations of HA during treatment in all groups (within group analysis) might be the results of: 1) neither net changes in HA metabolism in cartilage matrix nor release from joint fluid compartment during treatment, 2) inadequacy of the power of test due to high standard deviation of difference (σd) between pre- and post-treated serum concentrations, or 3) joint cartilage represents only a minority of body hyaline cartilage (less than 10%) and any changes in serum concentration of HA released from the affected joint(s) in monoarticular or oligoarticular diseases during treatment might be masked by the greater proportion of HA released from the normal joints or other sources [84].

In this study, the mean serum concentrations of CS 3-B-3(+) and W-F-6 epitopes in all groups were obviously higher than the values previously reported in both normal subjects and patients with OA of knee [70]. The indifferences in mean serum concentrations of CS 3-B-3 and W-F-6 epitopes during treatment in all groups (within group analysis) indicate that all treatments do not alter metabolism of these CS epitopes in cartilage matrix or the release of these molecules from the joint fluid compartment. However, similar to the case of HA, indifferences due to inadequacy of power of test could not be ruled out. These insignificant changes in serum concentrations of HA as well as CS 3-B-3(+) and W-F-6 epitopes from baseline during treatment in all groups suggest that all active treatments in this study may not modify the progression of OA.

However, recent study [85] has demonstrated that the chondroprotective agent, N-acetyl-D-glucosamine (NAG), improves clinical symptoms of OA. In addition, mean serum concentrations of CS 3-B-3(+) epitope in patients received NAG is lower than that in placebo group, suggesting that NAG may help to reduce the degradation of joint tissue chondroitin 6-sulphate proteoglycans in OA. Thus, investigation of the effects of chondroprotective agent in combination with other treatments (e.g., NSAIDS, EA, etc.) in order to seek a better treatment which can improve both OA symptom and cartilage metabolism is warranted.