

ELECTROACUPUNCTURE, MORPHINE AND CLONIDINE : A COMPARATIVE STUDY OF ANALGESIC EFFECTS

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Abstract : This is a comparative study of the analgesic effects of the modified traditional method of analgesia, electroacupuncture (EA), a standard analgesic drug, morphine, a potential analgesic drug, clonidine and the combination of EA + morphine and EA + clonidine. In each case, the index of analgesia (IA) was determined by recording the tail flick latency (TFL) in 60 rats divided into 6 groups of 10 rats each.

Group I rats served as control group while Group II-VI were subjected to EA for 20 min (at Zusanli and Kunlun points), morphine (5 mg/kg bw ip), clonidine (150 µg/kg bw ip), EA + morphine and EA + clonidine respectively. TFLs were recorded after the procedure and at 10 min intervals for 150 min or till the TFL returned to the baseline.

The IA, analyzed using the Kruskal-Wallis test and its significance determined by multiple comparison test (at 5% level), was found to be significantly different, at various time intervals, in the 6 groups studied.

Key words : electroacupuncture morphine clonidine
tail flick latency index of analgesia

INTRODUCTION

Acupuncture, the ancient Chinese art of healing has become popular throughout the world, especially in the past few decades. In the treatment of many diseases which are resistant to the conventional forms of therapy, acupuncture has proved to be remarkably effective (1, 2). Besides being free from the side effects commonly encountered in drug therapy, it is a safe, simple, effective and economical technique. Slowly but surely it is being absorbed into the mainstream of modern medicine, even though its philosophy could be bewildering to the modern western trained physician (3).

Research in acupuncture, as also electroacupuncture and stimulation-produced analgesia in general has shed light on the phenomenon of pain and its control. With recent advances in the understanding of pain transmission, it is now speculated that acupuncture and other stimulations may well liberate chemical mediators (endorphins) that can interfere with the transmission of nociception (4). Studies in literature show that acupuncture analgesia is a comprehensive result of multifactors, and hence further studies are required to understand the interactions between endorphins and the non-endorphin and other neurotransmitters in the mechanism of acupuncture induced analgesia.

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In the present study, the effects of electroacupuncture (EA) are compared with the analgesia produced by a standard analgesic drug, morphine, and a relatively new analgesic drug, clonidine, basically an anti-hypertensive drug, but subsequently found to have analgesic and sedative properties. The study also explores the possibility of synergism between the drugs and EA.

METHODS

The above study was carried out on 60 male albino rats (Wistar strain) in the weight range of 200-225 g, housed in small groups and kept in a temperature regulated room with food and water served *ad libitum*. The rats were divided into 6 groups of 10 rats each designated as Group I to Group VI.

Group I: Served as the control group and was subjected to an intraperitoneal (ip) injection of 1 ml normal saline (0.9%) and two acupuncture needles inserted at random sites in the left leg.

Group II: Subjected to EA for 20 min, (at 40 Hz), at Zusanli and Kunlun points, in the left leg, of enough intensity to (just) produce twitch of the adjoining muscles.

Group III: Subjected to an ip injection of morphine in a dose of 5 mg/kg body weight.

Group IV: Subjected to an ip injection of clonidine in a dose of 150 µg/kg body weight.

Group V: Subjected to EA (same as in Group II) at the end of which given an ip injection of morphine (same as in Group III).

Group VI: Subjected to EA (same as in Group II) at the end of which given an ip injection of clonidine (same as in Group IV).

Morphine sulphate and clonidine hydrochloride were freshly prepared in 0.9% NaCl, where they are freely soluble. The desired dosage was given in 1 ml solution of normal saline for better dispersal and absorption in the peritoneal cavity as also the control

volume. The doses selected were on the basis of previous studies (14, 18, 19) and the practical justification of the doses selected was given by the results, in that, in our study, both the drugs given ip in the above doses evoked antinociception.

Tail flick test: The algometric test used in this study was the tail flick test in which changes in the latency of the tail flick escape from noxious heating of the tail skin was used to assess the antinociceptive effect of the above procedures (5).

Each rat was placed in a transparent plastic rat holder and had its tail laid gently across the nichrome wire coil of the Ephaptex Heater - timer unit. A timer initiated the passage of an electric current through the wire coil sufficient to heat it and cause the animal to normally flick the tail away from the coil and this latency was timed and designated the tail flick latency (TFL). Normal rats flicked their tail away from the heat source with a latency of 2.5 - 4 sec.

A cut-off time of 10 sec was employed to avoid damage to the tail skin and if at the end of 10 sec the animal had not moved the tail it was removed by the experimenter. The heat stimulus was always applied to the tail between 4 and 6 cm from the tip.

The TFLs (in sec) were recorded at intervals of 10 min until a stable baseline was reached for each animal meaning 3 consecutive TFLs between 2.5 - 4 sec. Once the baseline was obtained the required procedure was carried out and the TFL recorded immediately after and thereafter at 10 min intervals for 150 min or till the TFL returned to the baseline value. The latencies recorded were normalized to an Index of Analgesia (IA) using the formula:

$$IA = \frac{\text{TFL} - \text{baseline TFL}}{10 - \text{baseline TFL}}$$

where TFL is the observed tail flick latency, baseline TFL is the mean latency for each animal before the procedure and 10 is the cut-

off time in sec. This formula gives a value of 0.0 if there was no change from the baseline value and 1.0 if the maximal inhibition of the tail flick was seen.

Results were presented as graphs of averaged IA values against time for all the groups of animals and the area under the mean curve was calculated (Fig.1). The data were

2. TFL changes were insignificant in the control Group I indicating the absence of analgesia. There were also no progressive changes in the TFL indicating the absence of sensitization of the tissues with repeated testing (Fig.1).

3. Table I depicts the significance by multiple comparison of the 6 groups at 30 min time

AREA UNDER THE MEAN CURVE

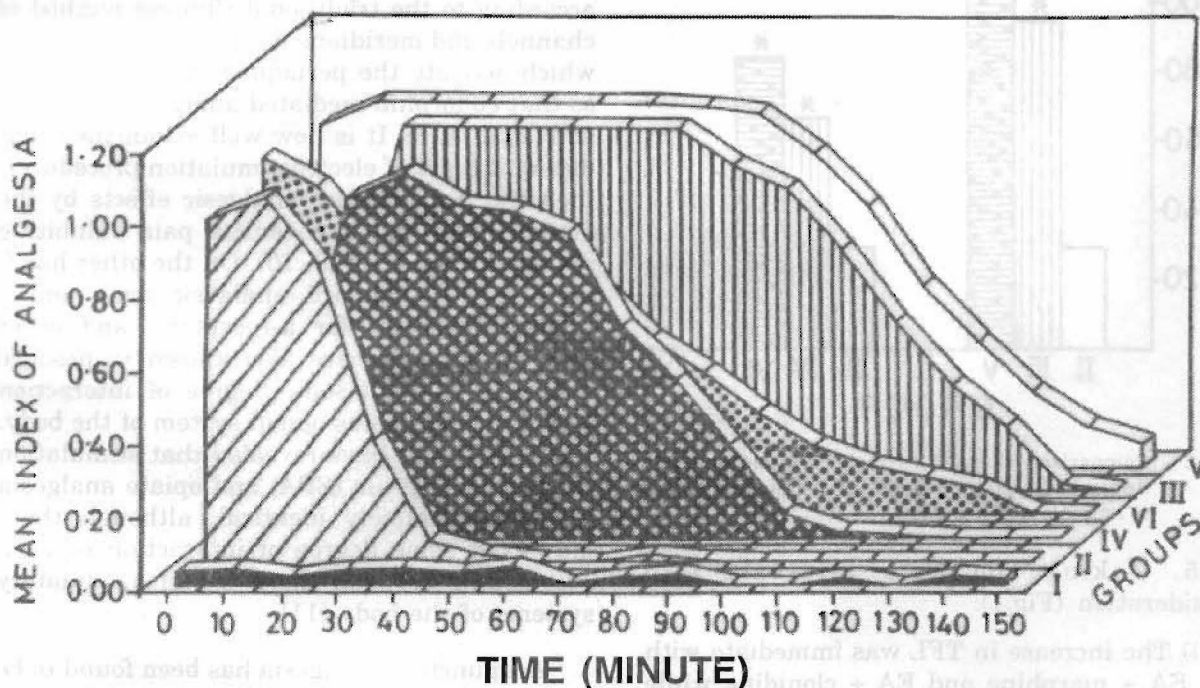


Fig. 1 : Area under the mean curve for all the groups of animals indicating their analgesic potential.

statistically analysed using the non-parametric test of Kruskal-Wallis and its significance determined by multiple comparison test (at 5% level).

RESULTS

1. TFL increased in all test groups i.e. Group II to Group VI, producing a significant increase ($P < 0.001$) in the IA in each group as compared to Group I thereby indicating their analgesic potential (Fig.1).

intervals from 0-150 minutes and shows significant difference ($P < 0.001$) between the groups at various time points.

4. Taking the area under the mean curve to be the index of efficacy of the technique used in modifying TFL, it was observed that the area was significantly more ($P < 0.001$) for morphine and clonidine as compared to EA thereby indicating both and particularly morphine to be a more potent analgesic. The area under the

mean curve of the combinations of EA + morphine and EA + clonidine were also significantly different ($P < 0.001$) from EA indicating a synergism between the processes and also from morphine and clonidine used alone ($P < 0.05$) (Fig.2).

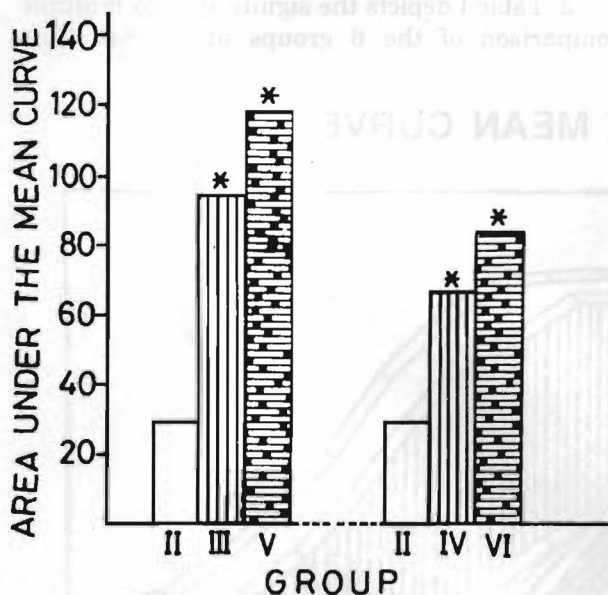


Fig. 2 : Comparison of the area under the mean curve (indicating analgesic potential) for the test group of animals. (* $P < 0.001$).

5. Taking the time intervals into consideration (Fig.1):

i) The increase in TFL was immediate with EA, EA + morphine and EA + clonidine while morphine and clonidine took 20 min to raise the TFL.

ii) The effect of EA was short lasting 68 ± 11 min while the effects lasted longest with EA + morphine (> 150 min).

DISCUSSION

The results of the present study have shown an increase in the TFL of the rat brought about by the administration of EA, morphine and clonidine, indicating their analgesic properties. In this study the combination of EA + morphine and EA + clonidine have shown a synergistic

effect proving that the analgesia brought about by EA is facilitated by the administration of morphine and clonidine.

Since the very beginning of recorded history, acupuncture has proved itself to be a powerful weapon against pain. It has been advocated as a successful mode of therapy for painful syndromes (2, 6) and its successful use in the field of surgical analgesia has been amply reported in literature (1, 7). In acupuncture the insertion of needles at certain points selected according to the traditional Chinese method of channels and meridians produce painful stimuli which activate the periaqueductal gray (PAG), so that endorphin mediated analgesia system is activated (4, 8). It is now well established that different types of electrostimulation procedures, including EA, produce analgesic effects by the activation of the endogenous pain inhibiting systems of the body (9, 10). On the other hand, morphine, a standard analgesic drug and a prototype agonist for μ -receptors, and other exogenous opiates are also known to produce analgesia through some degree of interaction with the endogenous opioid system of the body. Further studies have revealed that stimulation produced analgesia (SPA) and opiate analgesia are not completely identical, although there may exist some degree of interaction or even overlapping between the two pain modulatory systems of the body (11).

Acupuncture analgesia has been found to be facilitated not only by endogenous opiate-like substances but also by neurotransmitters like 5-HT (serotonin), acetylcholine and catecholamine (including noradrenaline and dopamine) (12, 13). Electrical stimulation of brain stem noradrenergic nuclei produces analgesia (14, 15) and iontophoretically applied noradrenaline inhibits the discharge of dorsal horn neurons evoked by noxious stimuli (16, 17). Both findings suggest an intimate association of alpha adrenoceptors with antinociception. Clonidine, an imidazoliene has been shown to evoke analgesic response (18) in a variety of test procedures, presumably acting

TABLE I : Significance by multiple comparison of the index of analgesia of the various groups at different time points (P value < 0.001). Each group is significantly different from the groups in its column against the various time points.

<u>Group</u> Time (min)	I (Control)	II (EA)	III (Morphine)	IV (Clonidine)	V (EA + Morphine)	VI (EA + Clonidine)
0	II V VI	I III IV	VI II	II V VI	I IV	I III IV
30	III IV V	III IV V	I II	I II	I II	
60	III V	III V IV VI	I II	II	I II	II
90	III V	III V	I II		I II	
120			IV	III V	IV	
150			V		III	

as an agonist at the presynaptic alpha 2-adrenoceptors in the spinal cord as well as in supraspinal structures of the central nervous system (19). Furthermore, several selective alpha 2-agonists have been shown to evoke antinociceptive response in laboratory animals (20). Systemic or spinal administration of clonidine produces profound antinociception in animals (21, 22) which is antagonized by alpha - blocking agents but not by naloxone (23). Early reports in humans have shown that intravenous injection of clonidine relieves post operation pain (24). Profound analgesia is produced by intrathecal clonidine in cancer related pain that was resistant to intrathecal administration of morphine (25, 26). Epidural clonidine has been found to be effective in neurogenic (27, 28) and post operative pain (29). In animals antinociceptive interactions between clonidine and morphine were found at the spinal level (30, 31). With intractable cancer pain, the combined spinal administration of

morphine and clonidine produce better pain relief than morphine alone (32). Bentley et al (33) have also suggested the possibility that the opioid receptor might be linked to its effector mechanism through alpha adrenoceptors. This possibility further substantiates the suggestion that a common pathway may be involved in the antinociceptive action of clonidine and morphine. Since EA also involves the opioid pathway in its production of analgesia this explains the synergism between EA and both morphine and clonidine.

Considerable knowledge about the phenomenon of pain and its control would be gained by going into the research on the scientific basis of acupuncture analgesia. It has been a useful research tool and has stimulated much thought and study. Used with care, as long as the patients are benefited without side effects and drugs, they should be given the benefit of acupuncture therapy.

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