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COMBINED OXYTOCIN AND ACUPUNCTURE AS A NOVEL REGIMEN FOR ANALGESIA FOR CANCER PATIENTS

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Oxytocin (OXT) is a neuropeptide with a peripheral role in reproduction, though it also may have a central effect. The aim of the study is to verify its analgesic role with and without acupuncture analgesia and to understand the mechanism of OXT in modulating pain process. Patients were divided into control, acupuncture, intrathecal OXT and combined intrathecal OXT+ acupuncture groups. Pain threshold, cardiovascular changes, and pain related mediators (serotonin, and dopamine) were assessed. A significant increase of the pain threshold was observed in intrathecal oxytocin group. The response was highly significantly increased in the combined group. Besides, OXT induces significant increase in the serum levels of neurotransmitters related to the pain. OXT proved to be more analgesic than auricular acupuncture and their combination provides a great synergistic analgesic effect.

Keywords: Oxytocin (OXT), neuropeptide, cardiovascular system, serotonin, and dopamine.

INTRODUCTION

Oxytocin, a neuropeptide produced primarily in the hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus (SON), has a wide range of impacts throughout the life cycle, resulting from activities both inside and outside the central nervous system[1]. It is already well recognized for its reproductive functions particularly during and after labor and delivery[2]. OXT, on the other hand, has been linked to antinociception, nervousness, eating, social behavior, and physiological stress, among other normal and pathophysiological activities[3].

Pain is a distressing subjective emotional sensation that occurs because of real or potential tissue injury. It's a major debilitating ailment that physiologists and doctors are always fascinated by Quesada *et al.*[4]. However, the neurological foundation for its propagation and processing is not well understood. According to the European Pain Federation EFIC, cancer survivors often experience pain as a symptom. Agony affects up to 40% of survivors, and at least 66 percent of those with advanced progressive cancer suffer from incapacitating pain[5].

Acupuncture is a very relevant old Chinese therapeutic method for treating pain[6]. He *et al.*[7] explained that auricular acupuncture is the treatment of choice for cancer patients suffering from pain. However, whether OXT and acupuncture work together to create better analgesia is not yet studied.

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Based on this background, the present study was designed to study the analgesic role of oxytocin with and without acupuncture analgesia and to understand the mechanism of OXT in modulating the pain process with highlighting on the clinical application of oxytocin, acupuncture, and their combination to relieve pain in cancer patients. In addition, this study aims to demonstrate the effect of oxytocin in modulating brain neurotransmitters as serotonin and dopamine and to understand the associated hemodynamic changes of administrating OXT on cancer patients' blood pressure and heart rate.

MATERIALS AND METHODS

The study is a perspective trial that included 24 patients. They were inpatients of cancer management department and outpatients attending outpatient pain management clinic of Assiut University Hospital. The study took place after approval of Local Ethical Committee and the patients signed an informed consent. The patients' ages were between (20 and 80 years). Patients who have contraindication for dural puncture as: local sepsis in the back or bleeding tendency or suffering from neurological diseases as brain and spinal cord infections or injuries was excluded. All patient included in the study received the usual regimen to relieve pain due to malignancy (MST: Morphine Sustained Tablets). The study was divided equally into four groups of patients: Group I (control group): received MST only, Group II (Auricular acupuncture analgesic patient group): had auricular acupuncture analgesia[8], Group III (Intrathecal OXT analgesic patient group): received 0.4 µg/kg oxytocin once intrathecally at 8 O'clock[9] and Group IV (Combined intrathecal OXT and auricular acupuncture analgesic group): received intrathecal oxytocin in addition to auricular acupuncture analgesia.

All patient groups were investigated to determine:

Pain severity

Pain severity in all patients was evaluated at the beginning and at the end of the study using: the numerical rating scale[10] and the visual analogue scale[11].

Cardiovascular changes

Blood pressure was measured by sphygmomanometer and heart rate was measured by counting the pulse over radial artery.

Sample collection and biochemical investigations

Blood samples (2 mL) were collected before and after injections. The whole blood was incubated to clot for 30 minutes in a clean screw-capped polypropylene tubes at room temperature and the serum was separated by centrifugation at 3000 rpm for 10 minutes. The separated serum was aliquotted and stored frozen in Eppindorff's tubes at -20°C until use. The serum collected was assayed for the levels of dopamine & serotonin before and after administration of the analgesic measure using specific enzymatic ELISA kits (Serotonin (5-HT) ELISA kit was purchased from WEKA MED supplies corp. (NY, USA) and dopamine ELISA kit was purchased from WEKA MED supplies corp. (NY, USA)).

Statistical analysis

Sample size was calculated using the Statstodo open access online calculator. The power calculation was based on expected results of previous studies[9]. Given an expected standard deviation of approximately 0.5, power = 0.80 and alpha = 0.05, 6 participants in each group were needed. Statistical analysis was carried out using SPSS (version 20). Data were analyzed non-parametrically and expressed in mean ±SD. First, to compare the difference between pre-and post-values using the Wilcoxon Signed Ranks Test. Second, to compare the differences between the control and other groups, the Mann/Whitney U-test was used. The level of statistical significance was $p< 0.05$ for all statistical evaluations.

RESULTS AND DISCUSSION

Results

The demographic and clinical data of the studied groups

This study included 24 cancer patients, divided into 4 groups:6 in each group. Out of the intrathecal OXT group, 2 (33.3%) were male and 4 (66.6%) were female. Their mean age was 42±15.4 years and mean body mass

index was 19.1±2.2 Kg/m². Out of the 6 combined intrathecal OXT+ acupuncture patients, 3 (50%) were male and 3 (50%) were female, with mean age 49.4±8.3 years and body mass index 18.1±3.2 Kg/m². Out of the control group, 4 (66.6%) were male and 2 (33.3%) were female, their mean age was 48±11.4 years and mean body mass index was18.8±2.9 Kg/m². While in acupuncture group, 3 (50%) were male and 3 (50%) were female, with mean age 48.4±11.4 years and mean body mass index were 18.1±2.9 Kg/m² (Table 1).

Changes in nociceptive tests

Comparison of pain intensity (in grades) using numerical rating scale (NRS) between different patient groups

Post-values of pain intensity in (II, III and IV) groups significantly ($p< 0.05$ and $p< 0.001$) decreased when compared to their pre-values. In addition, groups' II and III post-values were significantly ($p< 0.05$) lower than those of the control group. Moreover, mean post-value of group IV was significantly lower ($p< 0.001$) than post-value of the control. Their percentage changes from the control group were 22.2%, 31.9%, and 80.5% respectively (Table 2). In addition, there was a non-significant decrease ($p> 0.05$) in the comparison between post - values of group II versus III. However, post-values of group IV were significantly lower ($p< 0.001$) than post-values of group II and III (Fig. 1).

Comparison of pain severity (in millimeter) using visual analogue scale (VAS) between different patient groups

Post-values of pain intensity in groups (II, III and IV) cancer patients showed a significant decrease ($p< 0.05$ and 0.001) when compared to their pre-values. In addition, groups' II, III and IV post-values were significantly lower ($p< 0.05$; $p< 0.01$ and $p< 0.001$ respectively) than those of the control group. The percentage changes from the control group were 24.2%, 33.6%, and 81.05% respectively (Table 2). In addition, there was a non-significant decrease ($p> 0.05$) in the comparison between post-values of group II versus III. However, post-values of group IV were highly significantly lower ($p< 0.001$) than post-values of group II and III (Fig. 2).

Cardiovascular changes between different studied groups

Comparison between pre-and post-values of systolic and diastolic arterial blood pressure (per millimeter mercury)

Figure 3 (A, B) shows a non-significant change ($p> 0.05$) in both systolic and diastolic arterial blood pressure post values of all groups when compared to their pre-values. In addition, there was a non-significant ($p> 0.05$) change between groups II, III and IV and the control group. Regarding systolic blood pressure, the percentage changes in groups II, III, and IV from the control group were 4.1%, 2.5%, and 4.1% respectively (Table 2).

Table 1: Demographic and clinical characteristics in the different studied patients groups.

Item	Group I Control group (6 patients)	Group II Acupuncture group (6 patients)	Group III Intrathecal oxytocin group (6 patients)	Group IV Combined intrathecal oxytocin + acupuncture (6 patients)
Gender (males/females)	4\2	3\3	2\4	3\3
Age (years), mean ± SD	48.4 ± 11.4	46.4 ± 9.8	44.4 ± 15.4	49.4 ± 8.3
BMI (Kg/m²) mean ± SD	18.8 ± 2.9	17.9 ± 8.2	19.1 ± 2.2	18.1 ± 3.2

Data are presented as mean ± standard deviation. BMI=body mass index.

Table 2: Percent Change from the control group (group 1) values for the different measured parameters in different studied groups.

Parameter / % Change from control	Group II Acupuncture group (6 patients)	Group III Intrathecal oxytocin group (6 patients)	Group IV Combined intrathecal oxytocin + acupuncture (6 patients)
NRS (in grades)	22.2%	31.9%	80.5%
VAS (in millimeter)	24.2%	33.6%	81.05%
SBP (mmHg)	4.1%	2.5%	4.1%
DBP (mmHg)	2.5%	0%	2.5%
HR (beat/minute)	0.22%	1.34%	0.22%
Serum serotonin(ng/l)	59.6%	73.5%	92.7%
Serum Dopamine(ng/l)	25%	277.7%	347.2%

% Change from control= post value of each group- post value of control /post value of control x100. numerical rating scale (NRS), visual analogue scale (VAS), systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR).

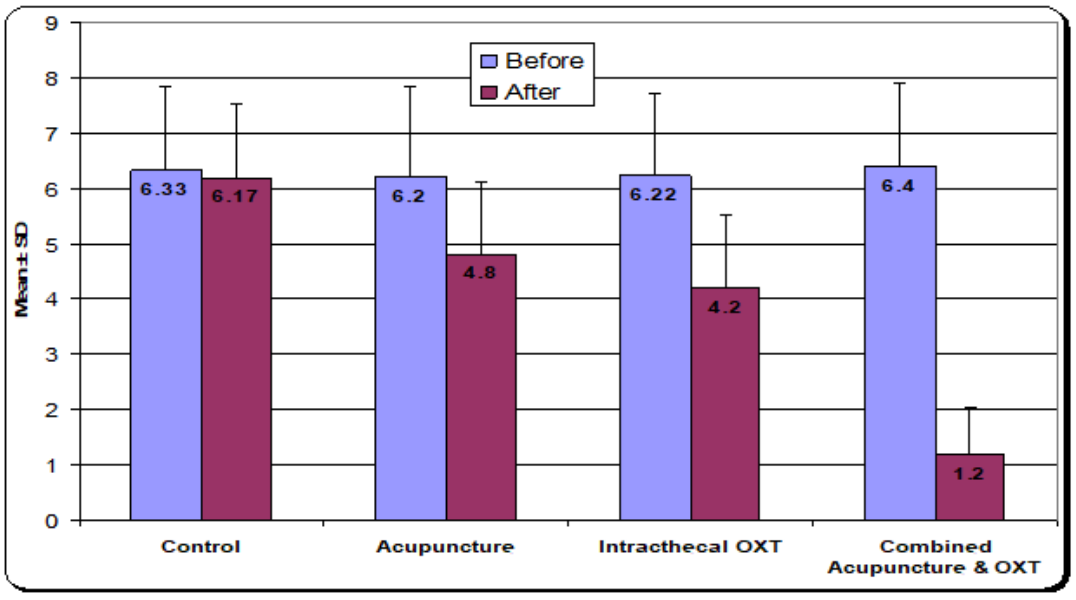

Fig. 1: Comparison of pain severity (in grades) using numerical rating scale (NRS) between different patient groups. Data expressed in mean ± SD.
: Comparison between before and after (Wilcoxon Signed Ranks Test) (< 0.05, ***< 0.001).
a: Comparison with Group I (Mann-Whitney Test). (a < 0.05, aaa < 0.001) b: Comparison with Group II (Mann-Whitney Test) (bbb < 0.001), c: Comparison with Group III (Mann-Whitney Test) (ccc < 0.001).

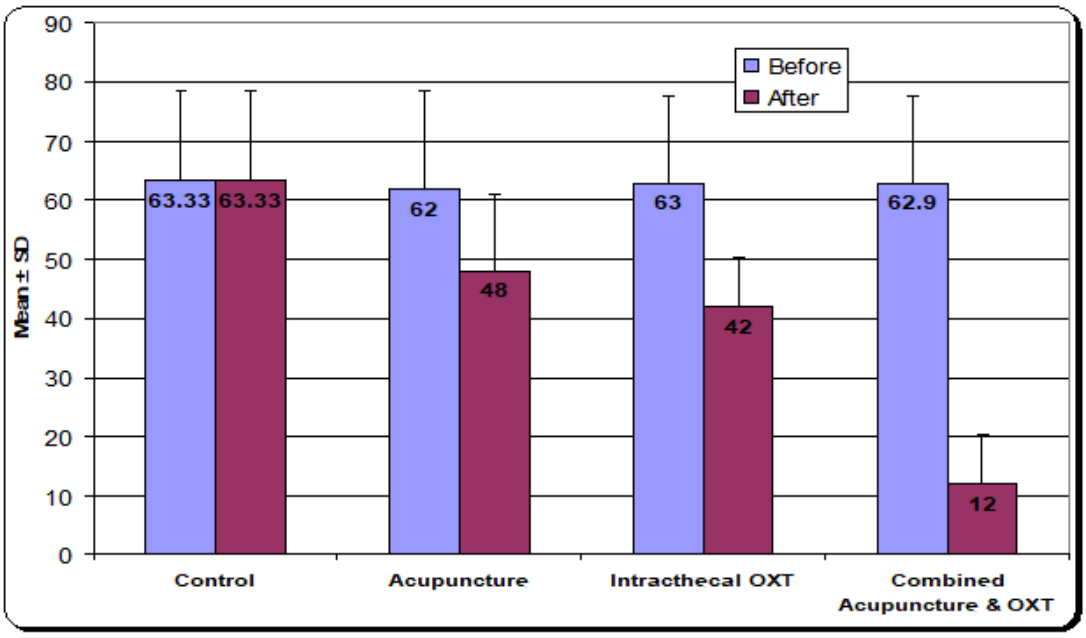

Fig. 2: Comparison of pain severity (in millimeter) using visual analogue scale (VAS) between different patient groups. Data expressed in mean ± SD.
: Comparison between before and after (Wilcoxon Signed Ranks Test) (< 0.05, ***< 0.001).
a: Comparison with Group I (Mann-Whitney Test). (a < 0.05, aaa < 0.001) b: Comparison with Group II (Mann-Whitney Test) (bbb < 0.001), c: Comparison with Group III (Mann-Whitney Test) (ccc < 0.001).

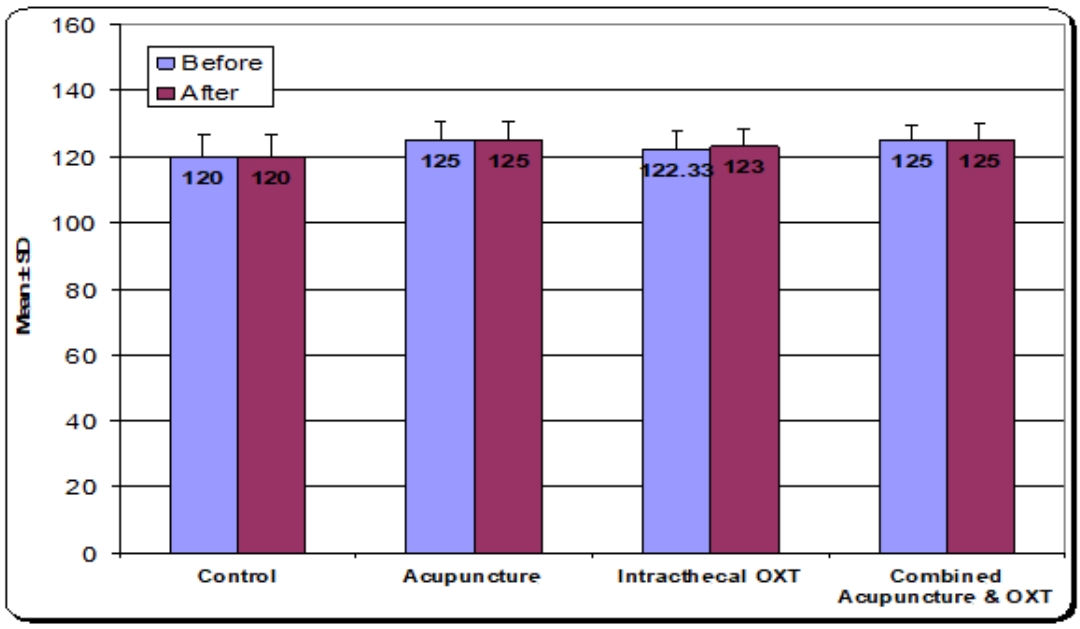

Fig. 3A: Comparison between pre-and post-values of systolic blood pressure (millimeter mercury) between different patient groups. Data expressed in mean ± SD.
: Comparison between before and after (Wilcoxon Signed Ranks Test) (< 0.05,*** < 0.001).
a: Comparison with Group I (Mann-Whitney Test). (a < 0.05, aaa < 0.001) b: Comparison with Group II (Mann-Whitney Test) (bbb < 0.001), c: Comparison with Group III (Mann-Whitney Test) (ccc < 0.001).

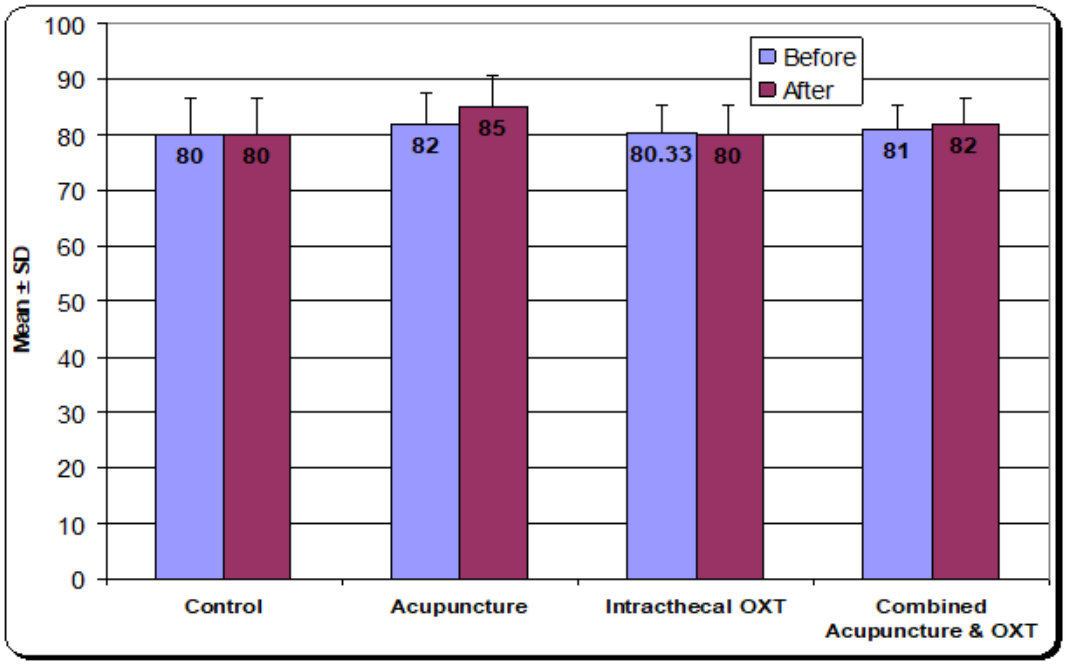

Fig. 3B: Comparison between pre-and post-values of diastolic blood pressure (millimeter mercury) between different patient groups. Data expressed in mean ± SD.
: Comparison between before and after (Wilcoxon Signed Ranks Test) (< 0.05, *** < 0.001).
a: Comparison with Group I (Mann-Whitney Test). (a < 0.05, aaa < 0.001) b: Comparison with Group II (Mann-Whitney Test) (bbb < 0.001), c: Comparison with Group III (Mann-Whitney Test) (ccc < 0.001).

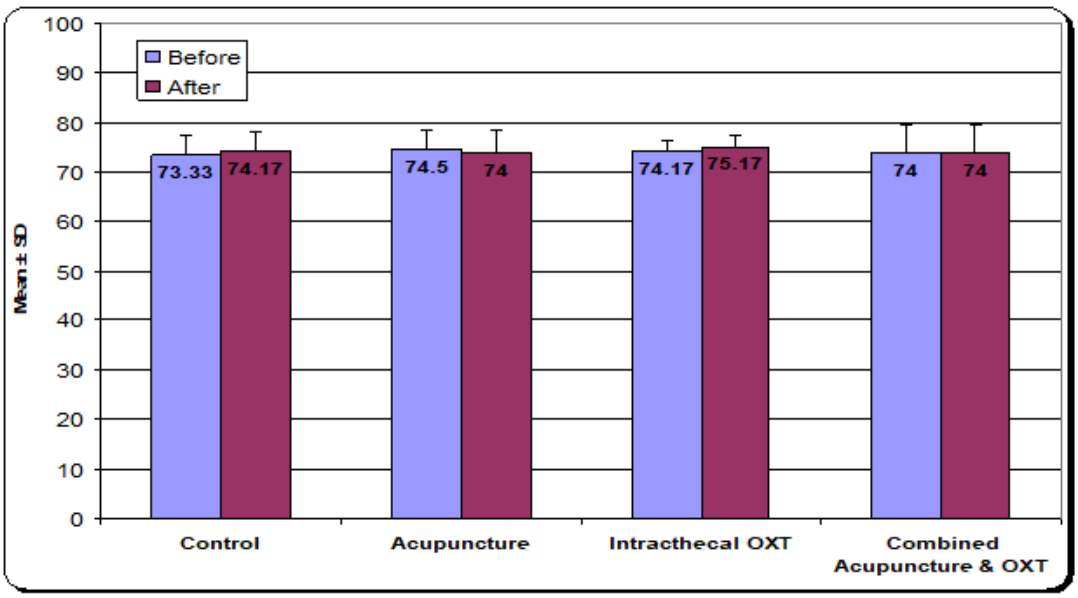

Fig. 4: Comparison between pre-and post-values of heart rate (beat/minute) between different patient groups. Data expressed in mean ± SD.
: Comparison between before and after (Wilcoxon Signed Ranks Test) (< 0.05, ***< 0.001).
a: Comparison with Group I (Mann-Whitney Test). (a < 0.05, aaa < 0.001) b: Comparison with Group II (Mann-Whitney Test) (bbb < 0.001), c: Comparison with Group III (Mann-Whitney Test) (ccc < 0.001).

While in diastolic blood pressure, the percentage changes in groups II, III, and IV from the control group were 2.5%, 0%, and 2.5% respectively (Table 2). There was a non-significant (p> 0.05) difference between post-values of group IV and those of groups II and III.

Comparison between pre-and post-values of heart rate (beat/minute)

Figure 4 shows a non-significant (p> 0.05) difference in post-values of heart rate measurement in all groups when compared to their pre-values and control group. The percentage changes in groups II, III and IV from the control group were 0.22%, 1.34%, and 0.22% respectively (Table 2). In addition, there was a non-significant change (p> 0.05) between the different studied groups.

Changes in biochemical parameters in different studied groups

Comparison between pre-and post-values of serum serotonin level (ng/l)

Statistical analysis of serum serotonin level in different studied groups are showed in figure 5. There was a highly significant decrease (p< 0.001) in post-values of the control group when compared to the pre-values. While groups' III and IV post-values were significantly (p< 0.001) increased when compared to their pre-values. However, post-values of group II showed a non-significant (p> 0.05) increase when compared to pre-values. The post-values of serum serotonin level in all studied groups were significantly (p> 0.001) higher than those of the control group. The percentage changes from the control group were 59.6%, 73.5%, and 92.7% respectively (Table 2). In addition, the group's IV post-values were significantly (p< 0.01) higher than post-values of groups II and III.

Comparison between pre-and post-values of serum dopamine level (ng/l)

Statistical analysis of serum dopamine level is showed in figure 6. It revealed a highly significant decrease (p< 0.001 and p< 0.01) in post-values of groups I and II when compared to their pre-values. While post-values of group III and IV significantly (p> 0.001) increased when compared to their pre-values. Post-values of group III and IV were significantly (p< 0.001) higher than those of the control group and group II. In addition, post-values of group IV were significantly higher (p< 0.001) than those of group III. The percentage changes from the control group in groups II, III, and IV were 25%, 277.7%, and 347.2% respectively (Table 2).

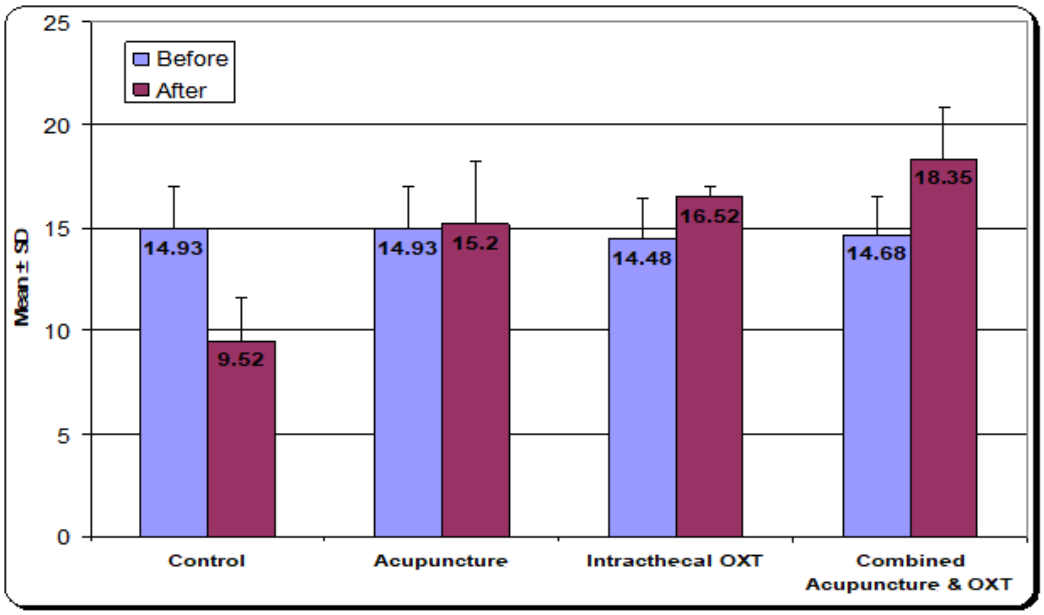

Fig. 5: Comparison between pre-and post-values of serum serotonin level (ng/l) between different patient groups. Data expressed in mean ± SD.
: Comparison between before and after (Wilcoxon Signed Ranks Test) (< 0.05, ***< 0.001).
a: Comparison with Group I (Mann-Whitney Test). (a < 0.05, aaa < 0.001) b: Comparison with Group II (Mann-Whitney Test) (bbb < 0.001), c: Comparison with Group III (Mann-Whitney Test) (ccc < 0.001).

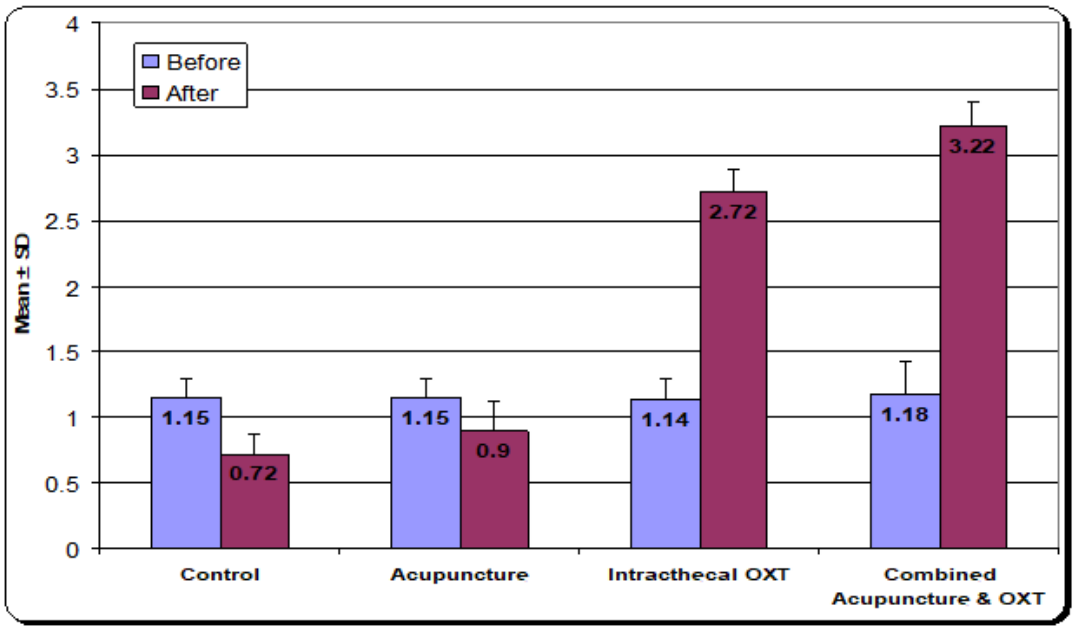

Fig. 6: Comparison between pre-and post-values of serum dopamine level (ng/l) between different patient groups. Data expressed in mean ± SD.
: Comparison between before and after (Wilcoxon Signed Ranks Test) (< 0.05, ***< 0.001).
a: Comparison with Group I (Mann-Whitney Test). (a < 0.05, aaa < 0.001) b: Comparison with Group II (Mann-Whitney Test) (bbb < 0.001), c: Comparison with Group III (Mann-Whitney Test) (ccc < 0.001).

Discussion

This work was done to clarify the analgesic role of oxytocin with and without acupuncture analgesia and to understand the mechanism of OXT in modulating the pain process with highlighting on the clinical application of oxytocin, acupuncture, and their combination to relieve the intractable pain in cancer patients. For this purpose, the present work included 24 patients who were randomly divided into four groups: control, auricular acupuncture, intrathecal OXT, and combined OXT and auricular acupuncture groups. In those patients, the international pain scales (visual analogue scale and numerical rating scale) measured pain severity. In addition, the biochemical parameters and the cardiovascular parameters were determined.

In the current investigation, intrathecal OXT and acupuncture were used to treat patients with cancer-related unbearable pain, and their analgesic effects were confirmed in agreement with a previous experimental trial[12]. Administration of EA, intrathecal oxytocin, or combination of both to patients with cancer intractable pain (groups II, III, and IV) resulted in a significant decrease in pain severity post-values when compared to pre-values measured by visual analogue scale (VAS) and numerical rating scale (NRS). The improvement was better with intrathecal OXT than that of EA. Also, the combination of both produced a highly synergistic response as shown in their percentage changes from the control value.

The previous findings go in line with previous studies done by Yang[9] and Flynn *et al.*[13] who reported that intrathecal oxytocin injection of 0.4 to 1.6 g/kg alleviated acute and chronic back pain. In a patient with persistent cancer pain, interventricular injection of OXT had an analgesic effect, lowering pain by 88 percent for 77 minutes. Furthermore, intranasal OXT has been shown to treat human headaches in a dose-dependent way. In addition, Ray[14] and So & Savidge[15] found that in patients with irritable bowel syndrome, oxytocin treatment raises intestinal pain thresholds.

In the current study, the application of acupuncture on cancer intractable pain patients' in-group II revealed improvement of their pain determined by international pain scales (VRS and NRS). The percentage

changes from the control group were 22.2% and 24.2% in both tests respectively. This goes with previous studies done by Xu *et al.*[16] who found that despite stable analgesic medication, some cancer patients who are in pain see a reduction in pain intensity after auricular acupuncture[17].

Auricular acupuncture is a non-invasive, successful, and easy analgesic technique performed on women with breast cancer to treat painful symptoms by tumors[18] or chemotherapy[19]. He *et al.*[7] explained that auricular acupuncture is the treatment of choice for cancer patients suffering from pain. The authors hypothesized that trying to press on the ear acupoint activates subcutaneous nerve endings, which reduce substance P and potentially trigger the brain produces pain and mood mediating chemicals (endorphins, enkephalins, glycine, glutamine, and GABA), which operate on various tissues and parts of the body, influencing their stress response and unpleasantness[20].

There is no available literature recording the use of combined OXT and EA to ameliorate pain in cancer patients and the current work is the first study that tries to benefit from the analgesic effect of this combination. The pain intensity mean post-value was significantly improved in-group IV in comparison to the pre-value. The percentage changes from the control group measured by NRS and VAS were 80.5% and 81.05% respectively. These findings confirm the present experimental results, which show a highly significant increase in pain threshold in rats receiving this combination, in agreement with experimental studies on rats and mice done by Abd el-Rady *et al.*[12] and Yang *et al.*[21]

The recorded levels of pain-mediated neurotransmitters (serotonin and dopamine) in the patient's serum of the present work, showed a significant increase of their post- values versus their pre-values in groups III and IV. Besides, these findings concur with the previous studies done by Abdelwahab *et al.*[2] and Grieb *et al.*[22] who found that the oxytocinergic system had a potential influence on the release of serotonin. In maternal depression, a link between the serotonin transporter (5-HTT) and the oxytocin receptor (OXTR) genes was discovered[23]. In addition, Beytollahi[24] recorded increase in dopamine level after intraventricular oxytocin administration.

While there was a significant decrease in post- value dopamine level and a non-significant increase in serotonin level when compared to their pre-values in-group II cancer patients who received acupuncture, the reduction of dopamine level may be contributed to severe depressive condition in cancer intractable pain patients as demonstrated by Zhou *et al.*[25] who reported that the chronic stressor depressive condition resulted in a significant decrease in the levels of serotonin, noradrenaline, and dopamine. Qiao *et al.*[26] explained the reduction in the serum levels of serotonin and dopamine recorded in the control patients' group of the present study.

Serum serotonin and dopamine post-values in-group IV cancer patients showed a highly significant increase when compared to pre-values. These findings concur with the improvement of pain and the release from its depressive effect in cancer patients (after administration of intrathecal OXT combined with auricular acupuncture) allowing an increase of the mood mediating neurotransmitters as serotonin.

The cardiovascular changes in the cancer patients involved of this study were carefully demonstrated to clarify any cardiovascular complications after using these analgesic measures. Application of acupuncture, intrathecal OXT and their combination on cancer patients' group II, III, and IV showed non-significant cardiovascular changes in the recorded systolic, diastolic blood pressure and the heart rate. This is in agreement with the pervious finding of Buemann and Uvnäs-Moberg[27], however, it is contradictory with a previous study by Wang *et al.*. This discrepancy may be attributed to the difference in locality of the used acupoint as acupuncture causes reduction in both arterial blood pressure and heart rate by activation of the parasympathetic nervous system, which initiates the relaxation response in adult cancer patients.

Conclusion

Accordingly, the administration 0.4 µg /kg oxytocin intrathecally is an effective dose to relieve the chronic intractable cancer pain with nearly no cardiovascular side effects. This effect is mediated through significant increase in serum serotonin and dopamine level (This study is first one clarifying the neurotransmitter mediators of the analgesic effect of OXT in human). Besides, OXT proved to be more analgesic than auricular acupuncture and their combination provide a great synergistic analgesic effect.

Ethics approval and consent to participate

The study protocol was performed according to the ethical guidelines of the Helsinki Declaration and was approved by the Research Ethics Committee of the Faculty of Medicine, Tanta University. Written informed consent was signed by all patients participating in the study.

Competing interests

The authors declare that there are no conflicts of interest.

Availability of data

All data are available on request.

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الجمع بين الأوكسيتوسين والوخز بالإبر كنظام جديد للتسكين لمرضى السرطان

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الأوكسيتوسين (OXT) هو ببتيد عصبي له دور هامشي في التكاثر ، على الرغم من أنه قد يكون له أيضًا تأثير مركزي. الهدف من الدراسة هو التحقق من دور الاوكسيتوسن المسكن مع وبدون استخدام الوخز بالإبر وفهم آلية عمله في تحسين الاحساس بالألم. تم تقسيم المرضى إلى مجموعة التحكم ، والوخز بالإبر ، والاوكسيتوسن داخل القراب ومجموعات الأوكسيتوسين + الوخز بالإبر داخل القراب. تم تقييم عتبة الألم ، والتغيرات القلبية الوعائية ، والوسطاء المرتبطة بالألم (السيروتونين ، والدوبامين). لوحظت زيادة كبيرة في عتبة الألم في مجموعة الأوكسيتوسين داخل القراب. تمت زيادة الاستجابة بشكل كبير في المجموعة المشتركة. إلى جانب ذلك ، يؤدي الأوكسيتوسين إلى زيادة كبيرة في مستويات المصل من الناقلات العصبية المتعلقة بالألم. أثبت الأوكسيتوسين أنه مسكن أكثر من الوخز بالإبر الأذني ، كما أن الجمع بينهما يوفر تأثيرًا مسكنًا تآزريًا كبيرًا.