

# **PREOPERATIVE PENTOXYPHYLLINE INFUSION ATTENUATES SURGICAL IMMUNE RESPONSE AND ALLEVIATES POSTOPERATIVE PAIN IN A DOSE-DEPENDENT FASHION DURING SURGICAL INTENSIVE CARE STAY AFTER PANHYSTERECTOMY.**

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## **Objectives:**

To evaluate the effect of preoperative administration of Pentoxifylline (PTX) on immune response to surgery and postoperative (PO) pain after panhystrectomy.

## **Patients & Methods:**

Forty-five female patients were allocated in 3 equal groups and received intravenous infusion of 100 ml of plain 0.9% NaCl as placebo (control group) or containing 5 or 10 mg/kg PTX, (groups PTX-5 and PTX-10, respectively). Infusion was given before induction of anesthesia with slow rate for 30 minutes. Duration of PO analgesia, total dose of PO morphine rescue analgesia and visual analogue scale (VAS) scores were determined for 24 hours PO. Serum levels of interleukin (IL)-10, IL-6 and tumor necrosis factor (TNF)- $\alpha$  were ELISA estimated preoperatively and at 6, 12 and 24 hours postoperatively during and after their surgical intensive care unit (SICU) stay.

## **Results:**

Mean total VAS pain scores were significantly lower with significantly longer PO duration of analgesia in PTX-10 compared to controls and to PTX-5 group with non-significant difference between PTX-5 and control groups. Total dose of rescue analgesia was significantly lower in PTX-10 group compared to control group and non-significantly compared to PTX-5 group. Both PTX groups showed significantly lower serum levels of TNF- $\alpha$  and IL-6 and significantly higher serum levels of IL-10 compared to control group with significantly lower serum levels of TNF- $\alpha$  and IL-6 and significantly higher serum levels of IL-10 with PTX-10 compared to PTX-5. The effects of PTX on serum IL-6 levels and IL-10 levels were significantly less at 24-hr samples compared to 12-hr samples. Control group showed significantly higher TNF- $\alpha$  and IL-6 and significantly lower IL-10 levels at 24-hr compared to levels 12-hr postoperatively.

## **Conclusion:**

Preoperative PTX infusion modulates the release of nociceptive cytokines with subsequent reduction of PO pain scores and analgesic consumption in a dose dependant fashion.

## Introduction:

Pain is an unpleasant sensation associated with varied consequences affecting the body systems. Acute pain is usually associated with both changes in hormonal and immune milieu manifested as release of stress hormones inducing tachycardia, hypertension, and decreased alveolar ventilation and may induce a cardiac insult. Postoperative pain as a phenomena, caused by a flow of nociceptive information occurs in two phases: Phase I is directly related to nociceptive stimulation that accompanies tissue injury during the operation, whereas Phase II, emerging after the operation, is the result of inflammatory response in the injured tissues and is caused by Phase I-induced changes in nociceptive structures of the nervous system,<sup>(1, 2, 3, 4)</sup>.

The data necessitated the ablation or prevention of such flow of nociceptive mediators, made preemptive analgesia mandatory. However, simple analgesics alone despite could abolish or lessens pain sensations could not modulate the release of pro-inflammatory cytokines that initiate and maintain the inflammatory cascade with its resultant stimulation of pain receptors at the injury site and sensitize the remote spinal or central receptors thus lowering their excitation threshold with aggravated pain sensation,<sup>(5, 6, 7)</sup>.

Thus, manipulation to blunt or minimize the release of pro-inflammatory cytokines could be considered as an analgesic modality using drugs without established analgesic properties. Pentoxifylline (PTX; 3, 7-diethyl-1-(5-oxo-hexyl)-xanthine), a methyl-xanthine, inhibits tumor necrosis factor (TNF) synthesis via the inhibition of phosphodiesterase and the increase of intracellular cyclic adenosine monophosphate (cAMP). It has also been shown to depress TNF production by macrophages at the transcription level. Moreover, PTX was found to markedly decrease neutrophil activation which plays a central role in the pathogenesis of adult respiratory distress syndrome and multiple organ failure,<sup>(8, 9, 10)</sup>.

This study was designed to evaluate the impact of preoperative administration of Pentoxifylline on cytokine response to surgery and postoperative pain parameters.

## Patients & Methods:

The present prospective comparative study was conducted at Kasr El-Ani University Hospital from

June 2006 till September 2010 and included 45 female patients assigned for panhysterectomy for non-inflammatory lesions.

Patients received preoperative preparation to keep their complete blood count to normal range and to abolish any infectious conditions judged by normal differential leucocytic count. Patients were randomly, using sealed envelopes, allocated in 3 equal (n=15) groups and received intravenous infusion of 100 ml of plain 0.9% NaCl as placebo (control group) or containing PTX at doses of 5 or 10 mg/kg, (PTX-5 and PTX-10, respectively). Infusion was given before induction of anesthesia with slow rate for 30 minutes. All infusions were freshly prepared preoperatively by an attending nurse and anesthesiologists were blinded about the infusion used.

All patients received a standardized anesthetic technique; anesthesia was induced with thiopental (3–5 mg/kg), fentanyl (2–3 µg/kg) and rocuronium (0.5 mg/kg). Balanced anesthesia was continued with isoflurane, fentanyl and rocuronium adapted to the patient's physiological reaction to surgical stimuli. After intubation of the trachea, the lungs were ventilated with 50% O<sub>2</sub> in air using a semi-closed circle system. Ventilation was controlled with a tidal volume of 8–10 ml/kg, and the ventilatory rate was adjusted to maintain an arterial partial pressure of carbon dioxide (paCO<sub>2</sub>) of 32–42 mmHg and arterial pH between 7.35 and 7.45. Intraoperative analgesia was provided in the form of nalofen ampoules, while muscle relaxation was maintained by repeated doses of pancuronium (1–2 mg). Central venous catheters were inserted routinely before surgery. At the end of surgery, neuromuscular blockade was reversed with neostigmine 40 µg/kg and glycopyrrolate 10 µg/kg. During the peri- and postoperative period, patients were continuously non-invasively monitored for mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP) and body temperature. Central venous pressure was maintained at 8–12 cm H<sub>2</sub>O by fluid replacement and blood transfusion was only given if blood loss exceeded 20% of the empirically estimated blood volume (75 ml/kg body weight). MAP was kept between 70 and 85 mmHg. To avoid hypothermia during the operative period, the patients were received pre-warmed fluids. All patients received 3<sup>rd</sup> generation cephalosporin as antibiotic prophylaxis after induction of anesthesia and was

continued postoperatively to guard against development of infection.

Postoperative pain was defined as a score  $\geq 4$  on a visual analogue scale (VAS) from 0 to 10 (where 0 = no and 10 = unbearable pain). Postoperative analgesia was provided on request (VAS  $>4$ ) in the form of IV boluses of 2.5–5 mg of morphine every ten minutes until they were comfortable, then, 5 mg morphine on request. Duration of PO analgesia, i.e., duration till request of first shoot of rescue analgesia, and the total dose of PO morphine used throughout the first PO 24 hours were determined. Patients were also followed-up for episodes of nausea, vomiting, pruritus or respiratory depression requiring medical treatment, time to mobilization (walking without assistance) and time to return of gastrointestinal motility in the form of return of bowel sounds and/or passage of flatus, occurrence of cardiovascular, pulmonary and infectious complications. Post operative surgical intensive care unit (SICU) discharge criteria were normal vital signs and adequate pain control with oral analgesics, absence of fever, and return of bowel function. Two days after surgery, the surgical wound was examined by the surgeon for wound infection, which was defined as a wound that was draining infected material requiring opening and packing. Time for removal of suction drains and suture was also defined.

Blood samples were withdrawn preoperatively (baseline), 6, 12 and 24-hrs after the end of surgery. Blood samples were allowed to clot and then centrifuged at 3000 rpm for 10 minutes and supernatant was separated and stored at  $-80^{\circ}\text{C}$  till ELISA assayed for serum levels of IL-10,<sup>(11)</sup> IL-6,<sup>(12)</sup> and TNF- $\alpha$ ,<sup>(13)</sup>.

### Results:

The study comprised 45 females with mean age of  $55.7 \pm 3.8$ ; range: 50-63 years and mean body mass index of  $29.5 \pm 1.6$ ; range: 27.4-33.3  $\text{Kg/m}^2$ . There was a non-significant ( $p > 0.05$ ) difference between patients distributed in the 3 groups as regards age, weight, height or body mass index. All surgeries were completed successfully and patients were transferred to SICU fully recovered with a non-significant ( $p > 0.05$ ) difference between the 3 groups as regards the operative time or the time spent in operating room, (Table 1). Follow-up data till hospital discharge showed non-significant difference between studied groups apart from the

earlier return of intestinal mobility in PTX-10 group that was significant compared to control group but was non-significantly shorter compared to PTX-5 group, (Table 2).

**Table (1):** Patients' and operative data

Group Data	Control	PTX-5	PTX-10
Age (years)	53.7 $\pm$ 2.7	57.6 $\pm$ 4.1	55.7 $\pm$ 3.6
Weight (Kg)	85.8 $\pm$ 5	85.8 $\pm$ 5	85.3 $\pm$ 2.3
Height (cm)	170.1 $\pm$ 2.2	170.1 $\pm$ 2.2	171.4 $\pm$ 2.8
BMI ( $\text{Kg/m}^2$ )	29.7 $\pm$ 1.8	29.7 $\pm$ 1.8	29.1 $\pm$ 1.1
Operative time (min)	127.7 $\pm$ 35.6	125.7 $\pm$ 34.9	128.3 $\pm$ 35.2
Operating room time (min)	139 $\pm$ 21	142 $\pm$ 14	141 $\pm$ 16

Data are presented as mean $\pm$ SD

Body mass index (BMI) = Weight (Kg)/ (Height in meter)<sup>2</sup>

**Table (2):** Postoperative data in the studied groups

Group Data	Control	PTX-5	PTX-10
SICU stay (hrs)	19.1 $\pm$ 3.7	18.3 $\pm$ 3.2	17.7 $\pm$ 3.5
Time till ambulation (hrs)	30.4 $\pm$ 11	28.2 $\pm$ 11.6	24.3 $\pm$ 7.4
Time till first flatus (hrs)	50.8 $\pm$ 12.3	41.2 $\pm$ 11.9	35.4 $\pm$ 8.2*
Hospital stay (days)	5.8 $\pm$ 1.9	5 $\pm$ 1.6	4.9 $\pm$ 1.9
PONV	5 (33.3%)	3 (20%)	3 (20%)
Wound infection	3 (20%)	1 (6.7%)	1 (6.7%)

Data are presented as mean $\pm$ SD & numbers; percentages are in parenthesis.

\*: significant versus control group

All patients required rescue analgesia; 22 patients (48.9%) requested it once, 17 patients (37.8%) required it twice and 6 patients (13.3%) requested it thrice. Number of patients received PTX-10 and requested rescue analgesia once was significantly higher compared both to those received PTX-5, ( $\chi^2=7.625$ ,  $p < 0.01$ ) and to controls, ( $\chi^2=25.5$ ,  $p < 0.001$ ) with significantly higher ( $\chi^2=3.282$ ,  $p < 0.05$ ) frequency of patients requested rescue analgesia once among those received PTX-5 compared to controls, (Fig. 1).

Mean total VAS pain scores were significantly lower in patients received PTX-10 compared to controls, ( $Z=2.988$ ,  $p=0.003$ ) and to those received PTX-5 infusion, ( $Z=2.235$ ,  $p=0.025$ ) with non-significantly lower VAS pain scores in patients received PTX-5 infusion, ( $Z=0.881$ ,  $p=0.378$ ) compared to controls. Mean duration of PO analgesia was significantly longer in patients

received PTX-10 compared to controls, ( $Z=3.128$ ,  $p=0.002$ ) and to those received PTX-5 infusion, ( $Z=2.536$ ,  $p=0.011$ ) with non-significantly longer duration of analgesia in patients received PTX-5 infusion, ( $Z=1.407$ ,  $p>0.05$ ) compared to controls, (Fig. 2). Total dose of rescue analgesia consumed was reduced in PTX-10 group significantly, ( $Z=2.310$ ,  $p=0.021$ ) compared to control group and non-significantly, ( $Z=1.155$ ,  $p>0.05$ ) compared to PTX-5 group, with non-significantly, ( $Z=0.933$ ,  $p>0.05$ ) lower rescue analgesia consumption in PTX-5 group compared to control group, (Table 3).

**Table (3):** Postoperative pain data in the studied groups

Group Data		Control	PTX-5	PTX-10
Postoperative pain VAS scores	1h	3.4±1.1	2.5±1.3	0.53±0.7
	2h	2.2±1.9	2.8±1.7	1.6±1.1
	4h	2±1.7	2.2±1.9	2.6±1.2
	8h	1.9±1.5	2.1±1.7	2.6±1.9
	12 h	2.1±1.2	1.8±1.4	0.7±1.1
	24 h	2.9±1.4	2±1.1	1.5±1.1
	Total	2.4±1.5	2.2±1.5	1.6±1.5*†
Times of request	Once	4 (26.7%)	7(46.7%)	11(73.3%)
	Twice	8 (53.3%)	6 (20%)	3 (20%)
	Trice	3 (20%)	2(13.3%)	1 (6.7%)
Duration of analgesia (hrs)		2±1.3	3.5±2.5	5.9±2.4
Total dose of rescue analgesia (mg)		9.7±3.5	8.3±3.6	6.7±3.1*

Data are presented as mean±SD, numbers & ratios; ranges and percentages are in parenthesis.

\*: significant versus control group.

†: significant versus PTX-5 group

Patients received PTX infusion showed significantly lower serum levels of TNF- $\alpha$  and IL-6 with significantly higher serum levels of IL-10 compared to control with significantly lower serum levels of TNF- $\alpha$  and IL-6 and significantly higher serum levels of IL-10 in patients received PTX-10 compared to those received PTX-5. However, the ameliorative effect of PTX on serum IL-6 levels and the stimulatory effect on serum IL-10 levels were significantly lessened at 24-hr samples compared to 12-hr samples, despite the non-significant elevation of serum TNF- $\alpha$  at 24-hrs compared to 12-hr levels. On contrary, control group showed significantly higher TNF- $\alpha$  and IL-6 and significantly lower IL-10 levels at 24-hr compared to levels estimated at 12-hr postoperatively, (Table 4).

**Table (4):** Serum levels of estimated cytokines in the studied groups throughout 24-hours postoperative

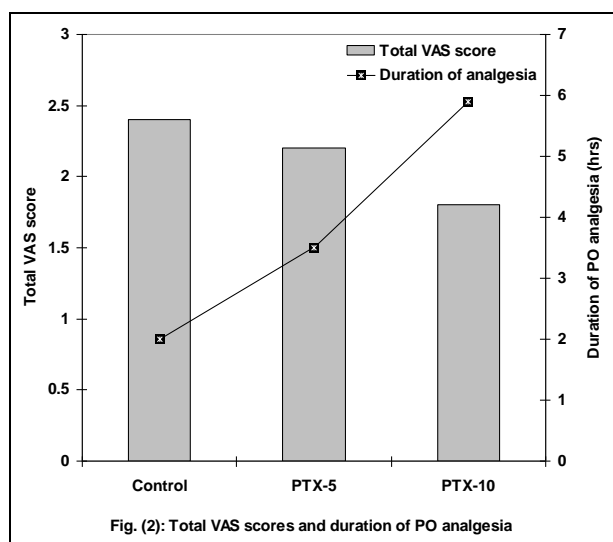
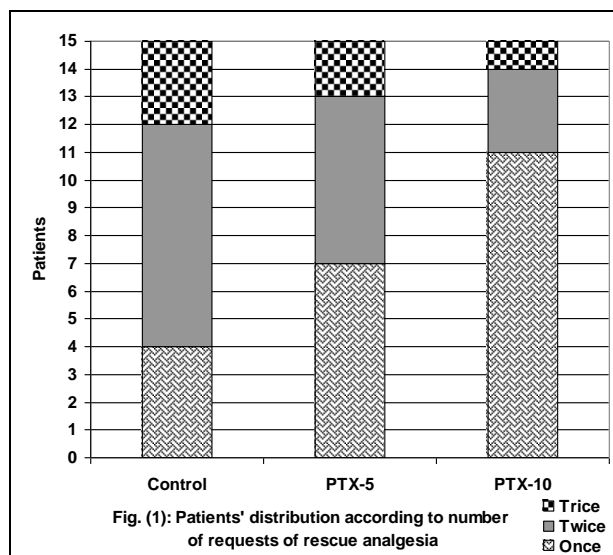
		Control	PTX-5	PTX-10
TNF- $\alpha$	Baseline	0.638±0.095 (0.5-0.85)	0.64±0.108 (0.52-0.85)	0.66±0.102 (0.54-0.87)
	6-hr	2.202±0.618 (1.2-2.95)	1.78±0.286 (1.2-1.95)*	1.4±0.32 (0.85-1.9)*†
	12-hr	2.393±0.414 (1.95-3.1)	2.09±0.428 (1.05-2.8)*	1.64±0.403 (1.05-2.35)*†
	24-hr	2.915±0.492 (2-3.85)‡	2.38±0.415 (1.3-3.05)*	1.98±0.82 (0.85-3)*†
IL-6	Baseline	63±17.4 (30-95)	60.1±13 (40-80)	61.7±9.5 (45-80)
	6-hr	102.7±13 (89-127)	89.5±8.1 (75-105)*	81.2±9.1 (65-93)*†
	12-hr	120.2±15.5 (95-154)	103.6±9.2 (84-116)*	93.1±8.4 (78-104.5)*†
	24-hr	203±49.4 (115-295)‡	150±14.8 (135-174)*†	136.8±15 (120-165)*†‡
IL-10	Baseline	21.2±6.6 (12-35)	22.1±5.9 (10-32)	21.5±4.5 (13-29)
	6-hr	24.5±7.9 (13-41)	30.5±5.6 (20-39)*	37.7±7.5 (29-53)*†
	12-hr	30.8±7.5 (20-46)	36.8±6.5 (29-51)*	48.4±9.7 (30-75)*†
	24-hr	23.3±3.4 (17-31)‡	30±5.8 (20-38)*†	39.4±8 (26-62)*†‡

Data are presented as mean±SD; ranges are in parenthesis.

\*: significant versus control group.

†: significant versus PTX-5 group

‡: significant versus 12-hrs level



### Discussion:

All patients showed significant increase, in comparison to preoperative levels, of serum levels of IL-10, IL-6 and TNF- $\alpha$  immediately after surgery, these results illustrate the effect imposed by surgery on cytokine response in the form of activation of the pro-inflammatory cytokine axis with the release of pro-inflammatory cytokines (TNF- $\alpha$  and IL-6) synchronized with the release of antagonistic anti-inflammatory mediators (IL-10) that precede the acceleration of acute phase protein production and thus modulate its extent. However, preoperative priming using PTX significantly reduced serum levels of TNF- $\alpha$  and IL-6 with concomitant significantly higher serum levels of IL-10 compared to control levels.

These data illustrate the effect of both priming and PTX infusion on cytokine release associated with surgical interference and go in hand with the

results of multiple clinical trials; *Coimbra et al.*,<sup>(14)</sup> reported that PTX down-regulates neutrophil activation and pro-inflammatory mediator synthesis with markedly decreased TNF- $\alpha$  production in patients with hemorrhagic shock treated with PTX added to resuscitation fluid. *Izadpanah et al.*,<sup>(15)</sup> found intravenous infusion of PTX administered preoperatively induced significantly lower postoperative plasma levels of TNF- $\alpha$  and IL-6 compared with the placebo receivers and could be applied to reduce inflammatory changes. *Iskesen et al.*,<sup>(16)</sup> reported increased plasma levels of TNF- $\alpha$ , IL-6, and IL-8 after cardiopulmonary bypass in patients received PTX and controls, with a greater increase in the control group and concluded that pretreatment with PTX before cardiac surgery inhibits pro-inflammatory cytokine release caused by cardiopulmonary bypass and has some beneficial effects in protecting the myocardium during the cardioplegic arrest period in open-heart surgery, without affecting postoperative hemodynamics. Various experimental and in vitro studies tried to explain the modulating effect of PTX on cytokine response in the form of suppressed production of proinflammatory and enhanced production of anti-inflammatory cytokines; *Ji et al.*,<sup>(17)</sup> attributed this suppressive effect on pro-inflammatory cytokines to inhibiting NF- $\kappa$ B activation, *Coimbra et al.*,<sup>(18, 19)</sup> attributed these effects either to direct inhibition of NADPH oxidase or inhibition of mitogen activated protein kinase phosphorylation, leading to decreased adhesion molecule expression and TNF- $\alpha$  synthesis, or to a significant decrease in NF- $\kappa$ B production.

Considering pain management as a major target for anesthetist, preoperative priming for abolishment or minimizing the release of nociceptive cytokines with subsequent reduction of pain severity is the main option of the current study. Preoperative priming using PTX provided significant reduction of PO pain scores with significantly longer PO pain free period and significant reduction of rescue analgesia. These findings were in line with *Izadpanah et al.*,<sup>(15)</sup> who found PTX intravenous infusion significantly reduced the use of narcotic analgesia with significantly lower pain intensity in patients who received PTX in comparison with those in the control patients undergoing nephrolithotomy; it causes no serious side effects.

The association between the lessened release of nociceptive cytokines and lower pain parameters after priming by PTX was established experimentally, **Nowak et al.**,<sup>(20)</sup> evaluated behavioral activity changes in response to acute and chronic nociceptive stimulus in rats and reported the effectiveness of PTX and concluded that the use of cytokine inhibitors might offer new strategies of drug-resistant chronic pain treatment. **Wei et al.**,<sup>(21)</sup> found tibia fracture chronically up-regulated TNF- $\alpha$ , IL-1 $\beta$  and IL-6 mRNA and protein levels in hindpaw skin and PTX treatment significantly reduced the mRNA expression and cytokine protein levels for all these cytokines, and inhibited the nociceptive sensitization and some vascular changes.

The reported significant reduction of serum levels of TNF- $\alpha$  and IL-6 with concomitant increased serum levels of IL-10 in PTX-10 group compared to PTX-5 group illustrated the dose dependency of PTX priming effect and supported that documented experimentally<sup>(22, 23)</sup> and could be attributed to the experimental results of **Ji et al.**,<sup>(17, 24)</sup> who reported that the inhibiting NF- $\kappa$ B activation is a dose-dependent activity of PTX.

However, one of the limitation of PTX infusion is its short-duration of action as manifested by peaking of its effect on examined cytokines was at 12-hr PO and started to decline significantly at 24-hr compared to at 12-hrs, despite being still significantly better compared to control group and significantly in favor of PTX-10. This may explain the non-significantly improved surgical outcome parameters with PTX infusion, apart from significantly shorter time till the return of gastrointestinal mobility. These findings go in hand with **Izadpanah et al.**,<sup>(15)</sup> who reported no significant difference in surgery time, length of hospital stay, and fever occurrence after operation during in-hospital follow-up among groups received PTX or controls.

The reported time-course effect of PTX supported that reported experimentally by **Ji et al.**,<sup>(26)</sup> who found PTX treatment significantly reduced the loss of overall retinal thickness and thinning of inner retinal layers with dramatic decrease in NF- $\kappa$ B activation, TNF- $\alpha$  and interleukin-1 $\beta$  production and mRNA expression, with the peak reached around 12 h. Also, **Ji et al.**,<sup>(24)</sup> found experimentally that an early, single dose of PTX dramatically reduced brain inflammation and apoptosis for up to 16-h post-injury.

It could be concluded that preoperative PTX infusion could be used as an adjuvant to modulate the release of nociceptive cytokines with subsequent reduction of PO pain scores with longer duration of PO analgesia and spared the use of PO narcotics. However, these beneficial effects are dose-dependent and peaked at 12 PO hours to start to significantly decline, so further wider scale studies were advocated to evaluate the outcome of repeated administration and to standardize the appropriate effective dose

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