

The Effect of Sodium Nitroprusside (SNP) as a Hypotensive Agent on Cytokine Release and Hormonal Response During Major Pelvic Surgery

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ABSTRACT

Background: The release of a variety of inflammatory mediators (cytokines) during surgery attempts to limit injury and spread of infection. Variation in anaesthetic technique may influence this cytokine balance and has important beneficial effects in promoting acute phase response and protection against viral and bacterial infection.

Aim of the work: This study was done to evaluate the effect of induced hypotension, using Sodium Nitroprusside (SNP), on proinflammatory cytokines (IL-6, IL-1 β and TNF- ∞) and hormonal response (cortisol, growth hormone and insulin) during major pelvic operations.

Patients and methods: This study was conducted on 40 patients scheduled for either radical cystectomy or anterior pelvic exenteration at the National Cancer Institute, Cairo University. They were randomly allocated to two groups: the control group, included 20 patients, where intra-operative mean arterial pressure (MAP) was maintained above 80 mmHg. The SNP group included 20 patients, where the MAP was maintained at 55-60 mmHg by an infusion of SNP. In both groups, premedication was the same, anaesthesia was induced with Na Thiopentone 5-7 mg.kg⁻¹ and pipecuronium 0.04 mg.kg⁻¹ and maintained with 0.8% isoflurane and 50% nitrous oxide in oxygen. Blood samples were obtained at four time points, namely T₁ in the morning before the operation, T₂: two hours after the induction of anaesthesia, T₃: two hours after the end of surgery, and T₄: 24 hours from T₁. Proinflammatory cytokines (IL-6, IL-1 β and TNF- ∞) and serum hormonal response (cortisol, growth hormone and insulin) were measured from each sample.

Results: The results of the present study demonstrated that all measured proinflammatory cytokines increased significantly 24 hours after surgery in both the study and control groups. The levels of the cytokines were significantly higher in SNP group. Serum cortisol concentrations increased in both groups, but reached higher level in SNP group at T₂ and T₃ compared to the control group. While growth hormone levels were higher in the control group at T₄. Serum insulin level decreased significantly during sur-

gery without marked differences between both groups observed at T₂ and T₃.

Conclusion: The present study offers evidence that induced hypotensive anaesthesia, using SNP infusion, exerted a stimulating effect on cytokine response to surgery. The used anaesthetic technique may have clinical implication in modifying the catabolic hormonal response to radical pelvic operations.

Key Words: Hypotensive anaesthesia - Sodium nitroprusside - Cytokines - Hormonal response.

INTRODUCTION

The importance of peri-operative cytokine balance and their role in modulating postoperative morbidity and mortality has received considerable attention [24].

These cytokines are low molecular weight polypeptides; synthesized and released by multiple cell types throughout the body. They have numerous actions, but primarily, they act as mediators of inflammatory process and as growth factors [18]. They have both local and systemic effects that attempt to limit injury and spread of infection. They also provide a suitable environment for tissue healing and repair [28]. Cytokines initiate their actions by binding to specific high affinity receptor complexes on the surface of target cells. Activation of these surface receptors leads ultimately to changes in the pattern of cellular RNA and protein synthesis [25].

Major cytokines synthesized after surgery are Interleukin-6 (IL-6), Interleukin-1 (IL-1) and Tumour necrosis Factor- ∞ (TNF- ∞). These pro-inflammatory cytokines are involved in the modulation of acute phase response and stimu-

lation of pituitary hormone secretion. Moreover, IL-6 is involved in immune response modulation [17,29].

Various studies have tried to determine how morbidity and mortality after anaesthesia and surgery may be affected by altering cytokine production and function [15,19].

Oka and his colleagues [22], in their study, demonstrated that IL-6 may be a sensitive marker of tissue damage and its level may be prognostic for predicting postoperative complications.

Many studies confirm that the choice of anaesthetic technique may influence cytokine balance [16,26]. Crozier et al. [2], demonstrated that general anaesthesia for major surgery induces an increase in the circulating IL-6. However, there was no data available on the possible effect of hypotensive anaesthesia on cytokine release and hormonal response to surgery.

Hypotensive anaesthesia is commonly used to reduce blood loss and provide better operative conditions, especially in abdominal and pelvic radical cancer operations, where severe blood loss may be expected [7].

The present study was designed to determine the modulatory effect of hypotensive anaesthetic technique, using Sodium Nitroprusside (SNP) as a hypotensive agent, on cytokine release and hormonal response during major pelvic surgery.

PATIENTS AND METHODS

The study was conducted after obtaining approval of the Local Ethics Committee of the National Cancer Institute (NCI), Cairo University. Forty patients (ASA physical status I or II) were included in the study after having their informed consent. Patients eligible for the study were those scheduled for either radical cystectomy operation or anterior pelvic exenteration. Exclusion criteria included history of cardiovascular, hepatic, renal or central nervous system dysfunction, patients taking steroids within 6 months before surgery and patients with hypertension, anaemia, or diabetes. In both groups, operations were selected to begin between 8:00 and 10:00 a.m.

One hour before induction of anaesthesia, all patients were premedicated with IV hyosine 0.006 mg.Kg⁻¹, midazolam 0.02 mg.Kg⁻¹ and

fentanyl 3 µg.Kg⁻¹. Upon arrival to the anaesthetic room, the radial artery was cannulated for continuous measurement of arterial pressure and a central vein was catheterized for administration of fluids in all patients undergoing hypotensive anaesthesia. A control blood sample was then collected for measurement of baseline concentrations of cytokines and hormones.

Anaesthesia was induced with sodium thio-pentone 5-7 mg.Kg⁻¹. Tracheal intubation was facilitated with pipecuronium 0.04 mg.Kg⁻¹.

Anaesthesia was maintained with 0.8% isoflurane and 50% nitrous oxide in oxygen. The lungs were mechanically ventilated to maintain normocapnea.

Then, patients were randomly allocated to one of two study groups. The control group (n = 20 patients) where mean arterial pressure (MAP) was maintained by fluid infusion above 80 mmHg. The hypotensive group (n = 20 patients) where intraoperative MAP was maintained at 55-60 mmHg by an infusion of sodium nitroprusside (Nipride 50 mg dissolved in 500 ml 5% dextrose in water in a dose range between 0.25-1.5 µg.Kg⁻¹.min⁻¹). Propranolol was given slowly up to a total dose of 0.05 mg.Kg⁻¹ and discontinued if heart rate slowed down to 50 beat.min⁻¹. Routine intraoperative monitoring included electrocardiography, pulse oximetry and end tidal carbon dioxide tension; this was maintained although the operative period. At the end of operation, the effect of muscle relaxant was antagonized and the tracheal tube was removed in the operating theater. Postoperative analgesia was provided according to patient's need and according to the protocol of pain control used at NCI.

Venous blood samples were taken four times: in the morning of the operation before surgery (T₁), 2 hours after the induction of anaesthesia (T₂), 2 hours after the end of operation (T₃) and the last blood sample was withdrawn the following day, 24 hours after surgery (T₄). Serum was separated and kept at -20°C in a sterile tube without anticoagulants. Proinflammatory cytokines (IL-6, IL-1β and TNF-∞) and serum hormones (cortisol, growth hormone and insulin) were measured in each sample.

Cytokines were measured using competitive enzymes immunoassay (EIA) by Accucyte® assay system (Predicta kits, Enzyme Diagnostic

Cambridge MA, USA). Cortisol was measured using the DSL-10-2000 Active™ cortisol EIA using Diagnostic serum laboratories INC.TX. Growth hormone was measured by immunoenzymatic assay (Biosource, Europe S.A.). Insulin was measured using the AXSYM insulin assay [microparticle enzyme immunoassay (MEIA). ABBOT Diagnostics].

Statistical analysis was done using SPSS-11. Means and standard deviations were used as a summary of quantitative data. Analytical tests used included paired *t* tests for comparing values at baseline and during follow up. A I-tail *t*-test was used for comparison of SNP group with control group. Significant level of < 0.05 was used throughout all statistical tests within the study.

RESULTS

Both groups were comparable with respect to patients' characteristics (age, weight and gender), as demonstrated in Table (1). All patients were subjected to radical cystectomy operations or anterior pelvic exenterations. Patients in the control group received significantly more intraoperative crystalloid and colloid infusions as compared to SNP-group (Table 1, $p < 0.05$).

MAP decreased in SNP-group after the start of infusion. However, both groups were comparable at the end of surgery without statistically significant difference in MAP (Fig. 1, $p < 0.05$). Heart rate (HR) also decreased in SNP-group, to levels which were significantly different statistically ($p < 0.05$) from the control group during surgery (Fig. 2).

Results in table (2) and fig. (3) show increase in the level of IL-6 at T₄ which was significantly higher in SNP group when compared to the control group ($p < 0.0001$).

TNF- α concentration increased to reach a maximum of 46.96 ± 0.03 and 34.6 ± 0.07 pg.ml⁻¹ at T₄ in both the control group and SNP-group respectively. These levels were statistically significant when compared to T₁ ($p < 0.05$). TNF- α concentrations were significantly higher in the control group, as compared to SNP-group ($p < 0.0001$) (Table 2, Fig. 4).

Both groups were comparable without statistically significant difference in IL-1 β concentra-

tions at T₂ and T₃. However, the level of IL-1 β increased significantly at T₄, to a level that was significantly higher in the control group ($p = 0.002$) (Table 2, Fig. 5).

Comparison between both groups as regard different hormonal levels is shown in Table (3). Serum cortisol concentration increased at T₂ and T₃ in both groups to levels which were significantly higher in SNP when compared to the control group ($p = 0.01$ and 0.004 , respectively) (Table 3 and Fig. 6). The concentration then started to decline to reach a level at T₄ which was statistically higher than the baseline value T₁ ($p < 0.05$).

Serum growth hormone concentration increased significantly to reach a level at T₄ which was statistically significant higher in the control group than SNP group (Table 3 and Fig. 7) ($p < 0.0001$).

Serum insulin level decreased gradually during surgery in both groups to levels which were significantly higher at T₂-T₃ in SNP group when compared to the control group ($p < 0.0001$ and $p = 0.01$, respectively). At T₄, both groups were comparable without statistically significant difference in insulin level, as demonstrated in Table (3) and Fig. (8).

Table (1): Patients' characteristics and intraoperative data.

	Control group n = 20	SNP group n = 20
Age (years)	47.3 \pm 5.9	49.1 \pm 6.2
Weight (Kg)	69.7 \pm 9.3	71.9 \pm 11.6
Gender (males/ females)	14/6	13/7
Duration of anaesthesia (min)	147.3 \pm 14.6	138.9 \pm 25.7
Duration of surgery (min)	126.1 \pm 29.6	116.4 \pm 24.4
Duration of hypotension (min)	—	96.5 \pm 11.7
Intraoperative crystalloid infusion (ml)	3190.6 (292.8)	2389 (229.6)*
Intraoperative colloid infusion (ml)	636.5 (193.2)	379.4 (216.4)*

Data are mean \pm SD * p -value < 0.05 , significant.

Table (2): Changes in the mean plasma cytokine concentrations in the two studied groups.

	Control group n = 20	SNP group n = 20
<i>Interleukin-6 (IL-6)</i> <i>pg.ml⁻¹:</i>		
T ₁	3.61±(0.19)	3.68±(0.21)
T ₂	4.37±(0.52)	5.62±(0.19)
T ₃	4.29±(0.87)	5.13±(0.96)
T ₄	19.12±(3.78)a	28.34±(7.12)a,b
<i>Tumour necrosis factor (TNF-α)</i> <i>pg.ml⁻¹:</i>		
T ₁	16.9±0.08	17.02±0.17
T ₂	29.8±0.06	18.6±0.09b
T ₃	29.42±0.05	18.9±0.04b
T ₄	46.96±0.03a	34.6±0.07a,b
<i>Interleukin-1β (IL-1β)</i> <i>pg.ml⁻¹:</i>		
T ₁	1.7±0.15	1.8±0.82
T ₂	1.8±0.06	1.7±0.46
T ₃	1.64±0.82	1.9±0.24
T ₄	24.79±1.94a	19.8±6.79a,b

Values are mean \pm SD.
 T₁ Preoperative value.
 T₂ 2h after induction of anaesthesia.
 T₃ 2h after the end of operation.
 T₄ 24h from T₁; a = Significantly different from T₁ in the same group; b = Significantly different from the control group.

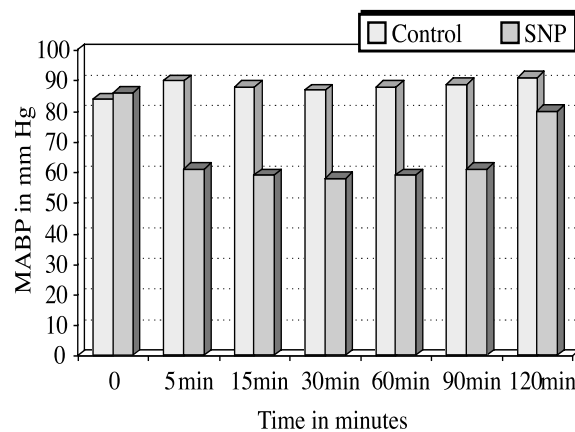


Fig. (1): Intraoperative mean arterial pressure.

Table (3): Changes of different hormonal concentrations in the two studied groups.

	Control group n = 20	SNP group n = 20
<i>Cortisol ($\mu\text{g.ml}^{-1}$):</i>		
T ₁	14.2±10.6	12.9±9.4
T ₂	16.9±11.7	24.3±7.8a,b
T ₃	31.2±13.4a	41.1±8.4a,b
T ₄	19.6±16.8a	23.4±6.9a
<i>Growth hormone ($\mu\text{U.ml}^{-1}$):</i>		
T ₁	1.22±1.68	1.48±0.97
T ₂	2.66±1.46	2.84±1.43
T ₃	2.73±1.39	2.76±1.28a
T ₄	7.92±2.73a	3.74±1.92a,b
<i>Insulin ($\mu\text{U.ml}^{-1}$):</i>		
T ₁	16.8±8.71	18.54±5.91
T ₂	10.32±2.27a	17.9±6.72b
T ₃	10.58±6.4a	14.93±4.84b
T ₄	8.37±5.23a	7.64±5.31a

Values are mean \pm SD.
 T₁ Preoperative value.
 T₂ 2h after induction of anaesthesia.
 T₃ 2h after the end of operation.
 T₄ 24h from T₁; a = Significantly different from T₁ in the same group; b = Significantly different from the control group.

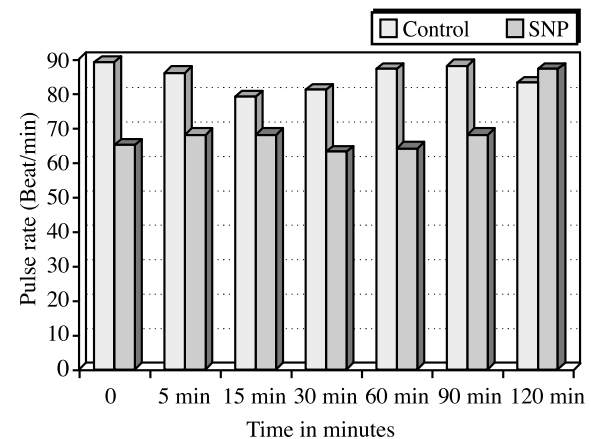
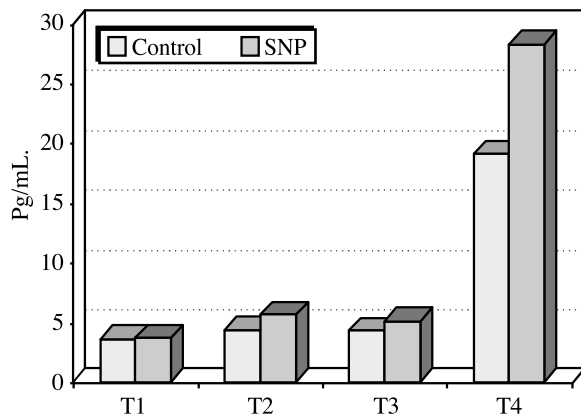
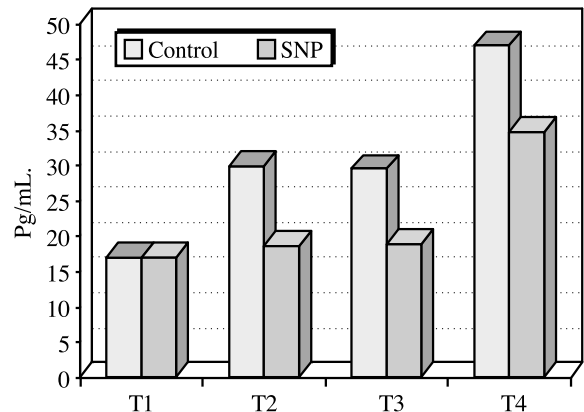


Fig. (2): Intraoperative mean changes in heart rate.



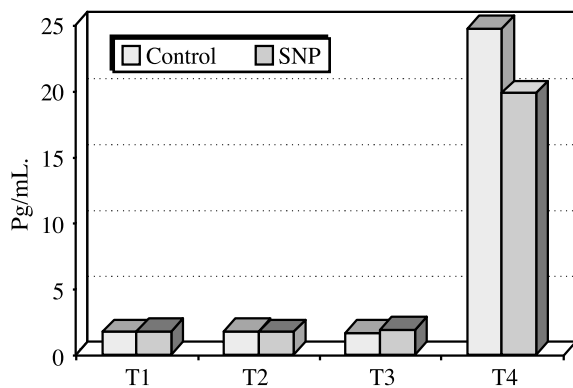
T1= Preoperative Value. T2= 2hours after Anesthetic induction. T3= 2 hours after the end of operation. T4= 24 hours from T1.

Fig. (3): Intraoperative mean changes in plasma IL-6.



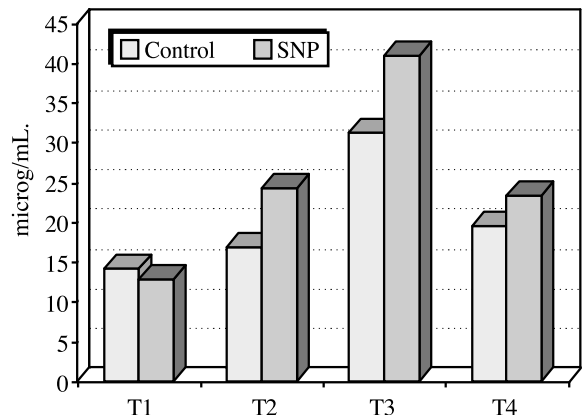
T1= Preoperative Value. T2= 2hours after Anesthetic induction. T3= 2 hours after the end of operation. T4= 24 hours from T1.

Fig. (4): Intraoperative mean changes in plasma TNF - alpha.



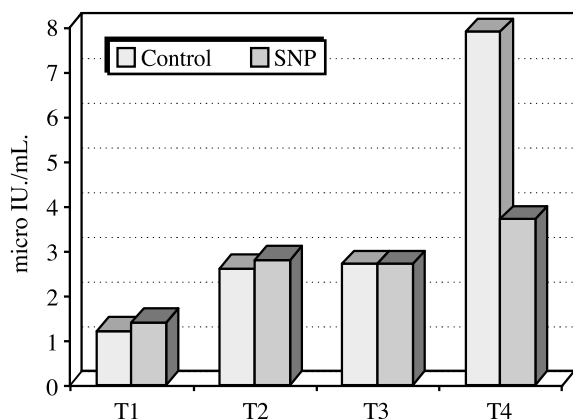
T1= Preoperative Value. T2= 2hours after Anesthetic induction. T3= 2 hours after the end of operation. T4= 24 hours from T1.

Fig. (5): Intraoperative mean changes in plasma IL - 1 Beta.



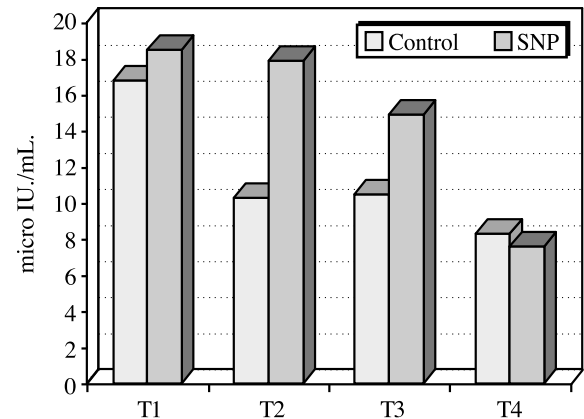
T1= Preoperative Value. T2= 2hours after Anesthetic induction. T3= 2 hours after the end of operation. T4= 24 hours from T1.

Fig. (6): Intraoperative mean changes in plasma cortisol levels.



T1= Preoperative Value. T2= 2hours after Anesthetic induction. T3= 2 hours after the end of operation. T4= 24 hours from T1.

Fig. (7): Intraoperative mean changes in plasma growth hormone.



T1= Preoperative Value. T2= 2hours after Anesthetic induction. T3= 2 hours after the end of operation. T4= 24 hours from T1.

Fig. (8): Intraoperative Mean changes in plasma insulin level.

DISCUSSION

Surgery commonly stimulates a cascade of events that mediate major immune alteration. Most of these changes are mediated by a variety of inflammatory mediators including cytokines [2]. Cytokines play an important role in the control of postoperative immunological functions and defense mechanisms [4].

At the present time, it is known that the choice of anaesthetic technique may influence cytokine balance. Modification of this balance is of great clinical relevance. Controlled hypotension has been used to reduce blood loss in major radical cancer surgery and hence the need for blood transfusion. Also, it is known to reduce bleeding during orthopedic, vascular, spinal surgery and radical prostatectomy [1,5,10].

In the current study, MAP was maintained at 55 to 60 mmHg in SNP group by changing the rate of SNP infusion [7]. SNP induced tachycardia was prevented by propranolol premedication [21].

The results of the present study illustrated that IL-6 plasma concentrations increased at T₄ in both groups compared to T₁. However, the increase was significantly higher in SNP-group as compared to the control group ($p < 0.0001$).

Helmy et al. [14], demonstrated elevation of IL-6 plasma concentration as a consequence of surgical trauma. This response reflects the extent of tissue damage and the severity of the operation. Nonetheless, in the current study, patients in both groups were undergoing the same type of surgery namely radical cystectomy or anterior pelvic exenteration. The surgical trauma could be considered comparable in both groups. Additional factors that might be responsible for the rise of IL-6 level may be the anaesthetic technique (induced hypotension) and/or the pharmacological effect of SNP-infusion.

The choice of anaesthetic technique might influence intraoperative cytokine balance by changing the typical stress response to surgery. Crozier et al. [2], demonstrated that alfentanil reduces IL-6 release after abdominal surgery. Heesen et al. [13], supported the result that SNP-infusion exerts an important additional stimulus for IL-6 release.

Liberation of nitric oxide (NO) from SNP

molecule activates guanylate cyclase enzyme found within vascular smooth muscle. This effect causes an increase in concentration of cyclic-guanosine monophosphate (c-GMP), which is an important intracellular second messenger molecule, involved in the process of IL-6 synthesis [23].

The elevation of plasma catecholamines (CA) by SNP should also be taken into consideration. CA stimulate beta 2 adrenoceptors expressed on the surface of monocytes which couple to adenylate cyclase enzyme [24].

IL-6 has a multifaceted role in the body response to injury and its lack may contribute to the immunosuppression associated with trauma and surgery [17]. IL-6 may act synergistically with other mediators to protect against postoperative viral and bacterial infection [24]. Furthermore, IL-6 may have a protective mechanism through stimulation of the full spectrum of acute phase response which elicit the release of adrenocorticotrophic hormones [11]. Thus modification of IL-6 secretion by SNP may be of beneficial clinical relevance.

Results showed that both TNF- α and IL-1 β were significantly increased in both groups at T₄. This increase was significantly higher in the control group than SNP-group. IL-1 β may be considered as an important cause for tissue damage and may contribute to chronic inflammation [15]. It may account for a variety of symptoms of rheumatoid arthritis when found in the synovial fluid [6]. IL-1 β also increases synthesis of prostaglandin E₂ (PGE₂) in the anterior hypothalamus, which may be responsible for hyperalgesia associated with inflammation [8].

TNF- α shares a central role with IL-1 β in initiating the cascade of inflammatory mediators, cytokines, complement and activation of leukocytes and macrophages [27]. They may also alter vascular permeability by interfering with the endothelial layer [4]. Their rise might be predictor of complications and tissue damage [9].

Sheeran and Hall [24], reported strong relation between endocrinal response to surgery and cytokines. They also assumed that cytokines play an important role as an afferent signal to stimulate the hypothalamo-adrenal axis,

acute phase response and stress response to surgery. In the present study, an increase in serum cortisol level was demonstrated in both groups in the postoperative period. However, cortisol level was significantly higher in SNP-group. Newton et al. [21], demonstrated that cortisol concentration increased earlier than IL-6. Naito et al. [20], assumed that IL-6 does not initiate the intraoperative cortisol response. However, it could be involved as a mediator of the persistent large concentrations of cortisol after operation and loss of the circadian rhythm observed in trauma patients [12].

Growth hormone concentration increased significantly at T₄ in both groups after surgery. This result was in accordance with the result of Moore et al., [19] who demonstrated rapid increase in G.H. secretion after major surgery. As regards insulin level, it decreases from preoperative level in both groups. This decline may be due to failure of insulin secretion to match the catabolic hyperglycemic response to surgery. This effect may be caused partially by α -adrenergic inhibition of β -cell secretion. In addition, there is a failure in the normal cellular response to insulin described by Desborough [3], as insulin resistance.

In conclusion, hypotensive anaesthesia with SNP seems to promote IL-6 production but not TNF- α or IL-1 β which showed significant decrease compared to the control group. Induced hypotension using SNP as a hypotensive agent can partly modify the endocrinal catabolic response to radical pelvic surgery which is often regarded as an indicator of stress-free anaesthesia.

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