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Research article

Ultrasound guided bilateral rectus sheath block and serum TNF-α and IL-6 after radical prostatectomy: A randomized double blinded study

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ABSTRACT

Background: General anesthesia can affect postoperative cytokine levels, leading to cellular immune inhibition following surgery. The primary objective of this study was to evaluate the effect of bilateral rectus sheath block on serum levels of TNF-α and IL-6 after radical prostatectomy.

Methods: Fifty patients undergoing radical prostatectomy, under general anesthesia were randomly allocated into two groups. Group RSB: A bilateral single shot of 20 ml plain bupivacaine 0.25% or 20 ml normal saline (Group C) in each side of rectus sheath. Postoperative pain was controlled by morphine as a rescue analgesia. Primary outcome was postoperative serum levels of TNF-α and IL-6. Secondary outcome measures: The total morphine consumption and evaluation of the visual analog pain score at 24 and 48 h postoperative.

Results: Both TNF-α and IL-6 were significantly lower in the RSB group at 24 h postoperative, the mean value of TNF- α was 76.26 ± 4.07 pg/ml in RSB group and 93.15 ± 6.90 pg/ml in the control group ($p < 0.001$), while IL-6 was 89.65 ± 13.00 and 102.6 ± 24.70 pg/ml in both groups respectively ($p = 0.01$). In RSB group, the visual analog pain score and the total morphine consumption were significantly lower ($p < 0.05$) during the first 24 h postoperative while, the first time requested for rescue analgesia was significantly longer ($p < 0.001$).

Conclusion: General anesthesia combined with bilateral rectus sheath block could decrease serum level of TNF-α and IL-6 after radical prostatectomy as well as decrease postoperative pain intensity with less opioid administration.

Clinical trials.gov ID: NCT03074097.

1. Background

General anesthesia can affect postoperative cytokine levels, leading to cellular immune inhibition following surgery [1]. Fortunately, anesthesia and analgesia for cancer surgery alters a minority of cytokines influential in regulating perioperative cancer immunity [2]. Analgesics used for control of postoperative pain like opioids, may suppress cellular and humoral immune function [3].

Prostate cancer is the most widespread cancer among male patients. Its development into metastatic condition rely upon growth factors, hormones and cytokines [4]. The release of cytokines such as IL-6 and IL-8 as a surgical inflammatory process, can lead to hyperalgesia by altering pain signal transmission [5]. IL-6 and TNF-a are the most important mediators of interactive signals, they associated with the progression of malignancy [6].

Schleich, (1899) Introduced the blockage of the rectus sheath (RSB) as a regional anesthetic technique that blocks the ventral branches of the seventh to twelfth intercostal nerves [7], to provide effective postoperative analgesia in patients undergoing major abdominal surgery [8]. Study rational: This study will help to find the correlation between rectus sheath block used for control of postoperative pain after radical prostatectomy and postoperative serum level of TNF-α and IL-6.

1.1. Research hypothesis

We hypothesized that an effective postoperative analgesia by sonar guided bilateral rectus sheath block, may help to inhibit the release of postoperative TNF-α and IL-6.

1.2. Aim of the study

The primary objective of this study was to evaluate the effect of the

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bilateral rectus sheath block on serum levels of TNF-α and IL-6 after radical prostatectomy. The secondary objective was to determine their association between the peripheral block and postoperative opioid consumption and pain intensity.

2. Methods

2.1. Study design

This study was prospective randomized double blinded, placebo-controlled, comparative clinical trial. The study was conducted at Assiut University Hospital between March 2017 and Januray 2018.

2.2. Ethical consideration

The study protocol was approved by the Institutional Review Board of our University and written informed consent was obtained from all subjects who participated in the trial. The trial was registered prior to patient enrollment at clinical Trials.gov ID: NCT03074097.

2.3. Inclusion criteria

Fifty male patients, aged over 40 years, classified ASA I or II with stage-III Prostate Cancer according to TNM staging, undergoing radical resection of cancer, prostate, through a midline abdominal incision under general anesthesia were included in the study.

2.4. Exclusion criteria

Patients with contraindications to rectus sheath block as patient refusal, coagulopathy, local infection and allergy to bupivacaine, planned transverse or oblique abdominal incision, extensive existing midline abdominal scarring, patients with chronic opioid use or pre-existing chronic abdominal pain were excluded from the study.

2.5. Randomization

The randomized study was performed using either group I or group II records that were placed inside the sealed envelopes before the study began and opened before induction of anesthesia by the physician who prepared the solutions with an equal size and determined that with the patient number. The solution was delivered to another doctor, blind to the content of the ready-made solution and was responsible for rectus sheath block. The responsible researcher remained blind to the selected group until the end of the study.

2.6. Rectus sheath block technique

Before anesthesia induction, the patients were lightly sedated with intravenous (IV) 0.5 mg/kg propofol, 0.01 mg/kg midazolam, and 1 μg/kg fentanyl. Under complete aseptic condition, the bilateral rectus sheath block was performed with ultrasonographic guidance using a 12 MHz linear probe (SONOACE R5; SAMSUNG MEDISON CO., Seoul, Korea), by a single anesthesiologist blind to the prepared solutions content. The probe was placed transversally at the level of umbilicus to visualize the rectus muscle. The needle was advanced in-plane from lateral to medial and superficial to deep, once the tip of an insulated needle was placed between the rectus abdominis muscle and the posterior rectus sheath using an 'in-plane' technique to visualize the entire needle, and after negative aspiration to avoid intravascular injection, the local anesthetic was injected on each side. Skin incision, was allowed 15 min after performing the technique.

2.7. Study groups

Patients were allocated to equal 2 groups 25 patients in each:

- Rectus sheath block group (RSB): 20 ml volume of plain bupivacaine (0.25%) was injected on each side.
- Control group (C): 20 ml of normal saline (0.9% Nacl) was injected on each side.

2.8. Anesthesia technique

One single anesthesiologist responsible for all the patients In both groups. The surgical team and technique (radical retropubic prostatectomy) were the same for every patient. Standard monitoring was performed by pulse oximetry, ECG, capnogram and non-invasive arterial pressure. A urinary catheter and nasogastric tube were inserted. After completion of the rectus sheath block, general anesthesia was induced by IV propofol (1–2 mg/kg) fentanyl 1 μg/kg IV; subsequently, the trachea was intubated with 0.5 mg/kg Atracurium IV and anesthesia was maintained with isoflurane in oxygen/air mixture and 0.5–1 μg/kg/hour fentanyl intravenous infusion (IVI) to maintain systolic blood pressure within the limit of 20% baseline value. At the end of the operation, anesthesia was discontinued and tracheal extubation performed once the patient was awake after reversing of the neuromuscular blocking agent and the patient was sent to the postoperative care unit after a full recovery for 48 h.

2.9. Postoperative analgesia

All patients, in the two groups received paracetamol 1 g/8h and ketorolac 10 mg/8h IV for 48 h postoperative. Morphine 0.1 mg/kg IV was given as a rescue analgesia when VAS was ≥ 3 or if the patient requested additional analgesia. A maximum of three doses of IV morphine were prescribed, with a minimum 8 h interval between the two consecutive injections.

3. Data collection

3.1. Demographic and operative data

Including age, weight, height, ASA classification, end tidal isoflurane concentration, intraoperative fentanyl consumption, duration of operation and discharge time from the hospital were recorded.

3.2. Measurement of TNF-α and IL-6

Four samples of 5 ml venous blood (preoperative and postoperative at one hour-one day – and two days postoperative) were drawn in plain tubes under sterile conditions from each patient. Serum was rapidly centrifuged and frozen at −70 °C until processed. TNF-α and IL-6 levels were estimated by enzyme-linked immunosorbent assay (ELISA) technique using commercially available kits from KOMA BIOTECH, KOREA.

3.3. Postoperative pain character

The time at which patient requested for rescue analgesia and the cumulative morphine consumption at 24 and 48 h were recorded. Evaluation of postoperative pain intensity; by Visual Analog pain Score (VAS) (0 = no pain, 10 = the worst pain imaginable) every 4 h during the first and second postoperative days were recorded. Patients were not being awakened during sleep and VAS was considered to be < 3.

3.4. Sample size calculation

A sample size calculation was performed by using G*Power version 3.1 and estimated with an expected difference in postoperative serum IL-6 of 12 pg/ml in the two groups at 5% level of significance and 90% power based on results from a previous study [6]. Two patients were added to compensate for violation of the study protocol, resulting in a total of 50 patients included in the study.

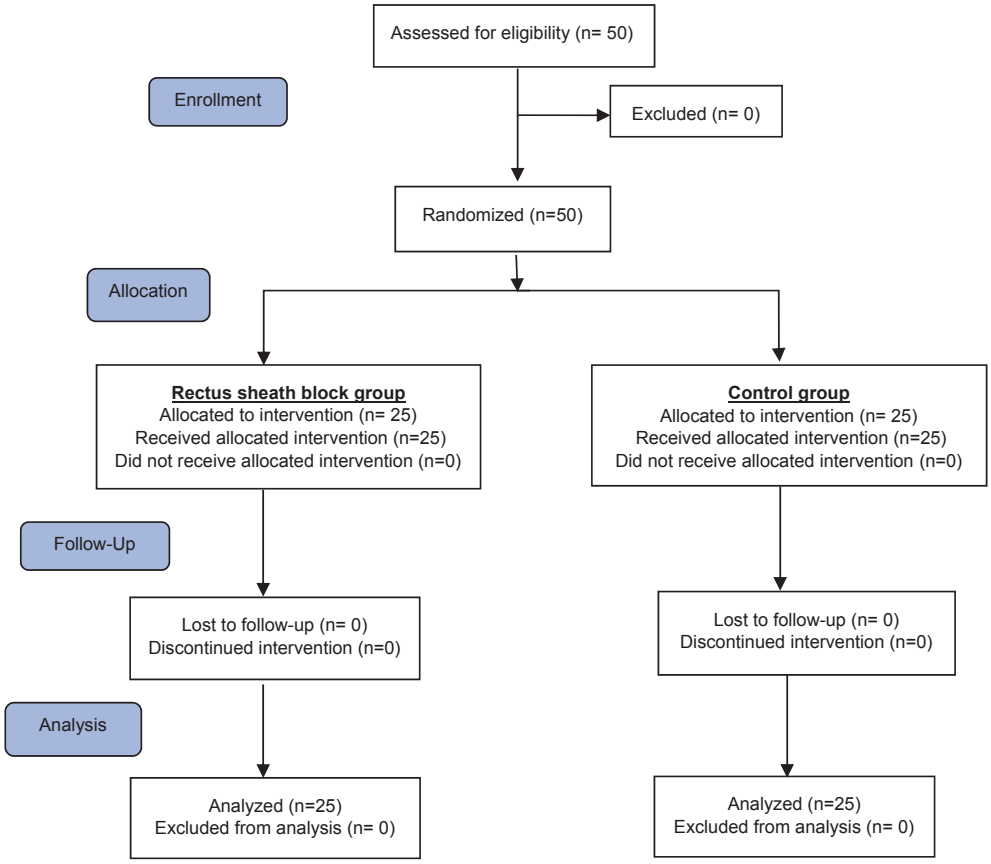

Fig. 1. Consort flow chart.

3.5. Statistical analysis

Collected data were analyzed using the statistical package SPSS version 20. Descriptive values were expressed as mean ± SD or number (%). For comparison between the two groups' student *t*-test and Mann-Whitney test was used as appropriate. P value was considered significant if < 0.05.

4. Results

Fifty patients were included in the study, 25 in each group; all the patients completed the study period (48 h postoperative) as shown in the Consort flow chart (Fig. 1).

4.1. Demographic and operative data

There were insignificant differences between the two groups as regard age, weight, height, ASA classification and duration of operation, while the end tidal isoflurane concentration ($p < 0.001$), intraoperative fentanyl consumption ($p < 0.001$) and the time to discharge from the hospital ($p = 0.012$) were significantly lower in RSB group as shown in Table 1.

Table 1
Demographic and operative data of patients in the study groups.

Item	Group, RSB (N = 25)	Group C (N = 25)	p-value
Age (year)	63.35 ± 8.34	65.20 ± 11.04	0.46
Weight (kg)	77.15 ± 6.50	78.90 ± 7.57	0.34
Height (cm)	171.42 ± 5.96	173.10 ± 6.92	0.31
ASA (I:II)	3:27	5:25	0.57
Duration of operation (hour)	3.24 ± 1.40	3.18 ± 2.14	0.89
End tidal isoflurane (%)	0.92 ± 0.12	1.14 ± 0.10	< 0.001*
Intraoperative fentanyl consumption (μg)	114.86 ± 29.9	233.73 ± 108.7	< 0.001*
Discharge time (days)	7.30 ± 1.8	8.83 ± 2.6	0.012*

Descriptive values were expressed as mean ± SD and ratio. *Significant p value < 0.05. Group, RSB: rectus sheath block with plain bupivacaine. Group C: rectus sheath block with normal saline (placebo group).

4.2. Serum TNF-α and IL-6 levels (Table 2)

The preoperative mean values of TNF-α and IL-6 showed insignificant differences between both groups. The mean value of TNF- α was 18.19 ± 2.81 pg/ml in RSB group and 18.31 ± 3.05 pg/ml in the control group ($p = 0.87$), while IL-6 was 20.42 ± 2.48 and 20.36 ± 2.32 pg/ml in both groups respectively ($p = 0.93$). Comparison between the postoperative values at different times, both TNF-α and IL-6 were significantly lower in the RSB group at 24 h postoperative, while at other times it showed insignificant differences. At 24 h postoperative the mean value of TNF-α was 76.26 ± 4.07 pg/ml in RSB group and 93.15 ± 6.90 pg/ml in the control group ($p < 0.001$), while IL-6 was 89.65 ± 13.00 and 102.6 ± 24.70 pg/ml in both groups respectively ($p = 0.01$).

4.3. Postoperative pain character (Table 3)

The cumulative morphine consumption: the mean value of total morphine consumed by the patients during the first day was significantly lower ($p = 0.0001$) in group RSB. During the first postoperative day it was 4.8 ± 0.6 mg compared to 32.3 ± 1.4 mg consumed in group C, while during the second postoperative day it was 9.7 ± 1.6 mg and 10.4 ± 1.3 mg in RSB and control group

Table 2
Serum level of TNF-α and IL-6 in the study groups; preoperative and at 1 h, 24 and 48 h postoperative.

Cytokines (pg/ml)	Group, RSB (N = 25)	Group C (N = 25)	P-value
TNF-α			
Preoperative	18.19 ± 2.81	18.31 ± 3.05	0.87
1 h postoperative	33.17 ± 2.32	34.73 ± 4.34	0.08
24 h postoperative	76.26 ± 4.07	93.15 ± 6.90	0.0001*
48 h postoperative	27.32 ± 2.04	28.14 ± 3.61	0.28
IL-6			
Preoperative	20.42 ± 2.48	20.36 ± 2.32	0.93
1 h postoperative	27.6 ± 3.07	28.13 ± 2.52	0.46
24 h postoperative	89.65 ± 13.00	102.6 ± 24.70	0.013*
48 h postoperative	49.12 ± 10.5	53.26 ± 12.04	0.16

Values were expressed as mean ± SD. * Significant p value < 0.05. Group, RSB: rectus sheath block with plain bupivacaine. Group C: rectus sheath block with normal saline (control group).

Table 3
Postoperative pain character during the first and second postoperative days in the study groups.

Item	Group, RSB (N = 25)	Group C (N = 25)	P-value
Total morphine consumption (mg)			
• 24 h postoperative	4.8 ± 0.6	32.3 ± 1.4	0.0001*
• 48 h postoperative	9.7 ± 1.6	10.4 ± 1.3	0.09
First time requested for analgesia (hours)	10.75 ± 3.7	0.77 ± 0.69	< 0.001*
Visual analog score			
• 24 h postoperative	1 (0–2)	3 (1–4)	< 0.001*
• 48 h postoperative	1 (0–2)	1 (0–3)	0.2

Values were expressed as mean ± SD or median (minimum-maximum). * Significant value < 0.05. Group, RSB: rectus sheath block with plain bupivacaine. Group C: rectus sheath block with normal saline (placebo group).

respectively, p value = 0.09 (insignificant difference). The first time patient requested for rescue analgesia was significantly longer (p < 0.001) in group RSB, it was10.75 ± 3.7 h, while in group C it was 0.77 ± 0.69 h.

Visual Analog Score (VAS): the mean value of VAS during the first postoperative day was significantly lower in group RSB (p < 0.001), while during the second postoperative day it showed insignificant differences between the two groups (p = 0.2).

5. Discussion

In this study single shot bilateral rectus sheath block with plain bupivacaine in patients undergoing radical prostatectomy through a midline incision under general anesthesia resulted in significantly lower postoperative serum TNF-α and IL-6 levels in the first postoperative day as well as fewer opioid consumption and less pain scores compared with those in the control group.

Both IL-6 and TNF-a, with same biological properties, and concerned in the development of cancer prostate [9]. High IL-6 levels were linked to advanced stage and morbidity associated with malignant tumour [10]. Thus, Scambia et al., since 1995; has been reported that patients with metastatic ovarian tumour and renal cell carcinoma have the highest IL-6 serum levels than those without metastasis [11].

Direct local production of IL-6 from malignant cells of prostate carcinoma significantly participate in elevated IL-6 serum level [12]. Michalaki and his colleagues (2004) hypothesized that the level of serum TNF-a and IL-6 is the prognostic sign of prostate cancer with respect to advancement to biochemical or symptomatic relapse depending on the results of serial values [6]

Purdy in his work 2016 found a significant association between numerical rating score and the serum levels of IL-10 and IL-1β following surgery, signifying a good relation between inflammation and pain [13]. There was a mutual interaction between pro-inflammatory cytokines and pain, where, pro-inflammatory cytokines adjust the sensitivity of pain, and the pain alters cytokine synthesis [14].

In their study, several authors indicated elevated plasma concentrations of IL-6 when surgery ended and on the first postoperative day [15]. Angst and his colleagues (2008) proposed that control of postoperative pain would lead to less hypersensitivity [16]. High pre or postoperative cytokine levels, particularly IL-6, is a predictor of outcome in different operative procedures [17]. After the surgical trauma, the cytokines are produced rapidly and its serum level increases in the postoperative period [18]. Increase in postoperative serum IL-6 level has been mentioned in many reports after gastrectomy for stomach cancer, [19]. However, its effect on morbidity was not analysed.

On their retrospective study Biki (2008) and Wuethrich (2010) reported that regional analgesia decreases the incidence of the recurrence of prostate cancer [20,21], on the opposite site, Tsui et al (2010), in their under powered study revealed that regional analgesia has insignificant effect on prostate cancer recurrence [22].

Jin et al., found that preoperative RSB maintain postoperative sleep through inhibition the release of IL-6 without affecting the analgesia [23]. While Purdy et al., concluded that RSB has no effect on the inflammatory response biomarkers concentrations in patients with benign or malignant disease [13].

5.1. Conclusion

Ultrasound guided bilateral rectus sheath block combined with general anesthesia associated with decrease serum level of TNF-α and IL-6 after radical prostatectomy. It also decreases postoperative pain intensity and the need for opioid administration.

5.2. Study limitations

The blood pressure was not invasively measured and recorded although the surgery was ultra-major. The systolic blood pressure was used as a single guide for narcotic administration and we did not use an objective analgesic monitor and this may affect the results. We did not use anesthesia depth monitor as BIS or Entropy to unify and stabilize the conditions that might affect the serum levels of cytokines and subsequently the results.

5.3. Recommendations

The authors recommend further studies to be performed on the same populations to evaluate the effect of the rectus sheath block on the long term postoperative serum prostate specific antigen for early detection of recurrence of cancer prostate.

6. Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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