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RESEARCH

A randomized-controlled trial assessing the effect of intraoperative acupuncture on anesthesia-related parameters during gynecological oncology surgery

Eran Ben-Arye[1,2] · **Irena Hirsh**[3] · **Yakir Segev**[2,4] · **Michael Grach**[3] · **Viraj Master**[5] · **Arie Eden**[3] · **Noah Samuels**[6] · **Nili Stein**[7] · **Orit Gressel**[1,2] · **Ludmila Ostrovsky**[4] · **Galit Galil**[1] · **Meirav Schmidt**[3] · **Elad Schiff**[2,8] · **Ofer Lavie**[2,4]

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Abstract

Context and objectives The present study examined the impact of intraoperative acupuncture on anesthesia-related parameters in patients undergoing gynecological oncology surgery.

Methods Participants underwent preoperative integrative oncology (IO) touch/relaxation treatments, followed by intraoperative acupuncture (Group A); preoperative IO treatments without acupuncture (Group B); or standard care only (Group C). Mean arterial pressure (MAP), heart rate (HR), MAP variability (mean of MAP standard deviation), bispectral index (BIS), and calculated blood pressure Average Real Variability (ARV) were measured intraoperatively.

Results A total of 91 patients participated: Group A, 41; Group B, 24; Group C, 26. Among patients undergoing open laparotomy, Group A showed lower and more stable MAP and HR compared to Group B, (MAP, $p=0.026$; HR, $p=0.029$) and Group C (MAP, $p=0.025$). Mean BIS, from incision to suture closing, was lower in Group A (vs. controls, $p=0.024$). In patients undergoing laparoscopic surgery, MAP was elevated within Group A ($p=0.026$) throughout surgery, with MAP variability significantly higher in Group A ($P=0.023$) and Group B ($P=0.013$) 10 min post-incision (vs. pre-incision). All groups showed similar intraoperative and post-anesthesia use of analgesic medication.

Conclusion Intraoperative acupuncture was shown to reduce and stabilize MAP and HR, and reduce BIS in gynecology oncology patients undergoing laparotomy, with no impact on perioperative analgesic medication use. In the laparoscopic setting, intraoperative acupuncture was associated with elevated MAP. Further research is needed to explore the hemodynamic and BIS-associated benefits and risks of intraoperative acupuncture, and the impact on the use of analgesic drugs in response to these changes.

Keywords Integrative oncology · Gynecological oncology · Acupuncture · Pain · Intraoperative · Integrative medicine

✉ Eran Ben-Arye
eranben@netvision.net.il

1 Integrative Oncology Program, The Oncology Service, Lin, Zebulun, and Carmel Medical Centers, Clalit Health Services, 35 Rothschild St, Haifa, Israel

2 Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

3 Department of Anesthesiology, Critical Care and Pain Medicine, Carmel Medical Center, Haifa, Israel

4 Department of Obstetrics and Gynecology, Carmel Medical Center, Haifa, Israel

5 Department of Urology and Winship Cancer Institute of Emory University, Atlanta, GA, USA

6 Center for Integrative Complementary Medicine, Faculty of Medicine, Shaarei Zedek Medical Center, Hebrew University of Jerusalem, Jerusalem, Israel

7 Department of Community Medicine and Epidemiology, Carmel Medical Center, Haifa, Israel

8 Department of Internal Medicine & Integrative Medicine Service, Bnai-Zion, Hospital, Haifa, Israel

Introduction

Many of the leading cancer centers across the globe are providing patients' complementary medicine within an integrative oncology (IO) setting (Ben-Arye et al. 2013). IO offers patient-centered and complementary care to patients, improving multiple domains of quality of life (QoL) while addressing clinical outcomes across the cancer care continuum (Witt et al. 2017). Clinical guidelines for the use of IO in the treatment of patients with breast cancer have been published by the Society for Integrative Oncology and endorsed by the American Society of Clinical oncology (Mao et al. 2022), as have guidelines for the use of these modalities for the treatment of cancer-related pain (Mao et al. 2022).

An increasing number of randomized-controlled trials have been published on the effective and safe use of IO interventions for the relief of chemotherapy-induced toxicities and improved QoL in the gynecological oncology setting. These include a head-to-head crossover study on the use of acupuncture for the prevention of delayed chemotherapy-induced emesis (Rithirangsriroj et al. 2015); and pragmatic trials which show greater adherence to paclitaxel-based treatment regimens among patients adhering to a weekly IO treatment program, with implications regarding treatment outcomes (i.e., survival) (Ben-Arye et al. 2022; Shalom-Sharabi et al. 2017; Segev et al. 2021). The findings of this research have led to the design of an integrative gynecological oncology model of care by a multi-disciplinary team of IO-trained practitioners, gynecological oncologists, medical oncologists, oncology nurses, and psycho-oncologists. The model seeks to ensure continuity of IO care throughout the patient's journey with cancer (Ben-Arye et al. 2016).

Despite the large body of research on IO models of care, little has been published on the impact of these models in the surgical gynecological oncology setting. This is most apparent with respect to the perioperative period, including the diagnosis and staging of the patient's tumor (Petersen and Quinlivan 2002). At the same time, the findings of the research on IO models in the treatment of patients with breast cancer during the perioperative period indicate a potential for pre- and intraoperative benefits which are relevant to the gynecological oncology perioperative setting. These include studies on acupuncture following mastectomy (Sharp et al. 2010); touch therapies at 6 weeks following breast surgery (Sharp et al. 2010); and the use of intraoperative electro-acupuncture to reduce postoperative pain following brain tumor resection (Liu et al. 2015).

The present study explored the impact of intraoperative acupuncture on anesthesia-related parameters in patients undergoing gynecological oncology surgery. The association between the effects of intraoperative acupuncture on postoperative pain has been shown in a previous analysis of the current study group, using patient-reported outcome measures to compare the effect of intraoperative acupuncture with controls (Ben-Arye et al. 2023). The current study set out to assess intraoperative anesthesia-related hemodynamic parameters, including mean arterial pressure and heart rate. This is with the goal of further understanding the mechanism through which intraoperative acupuncture may impact postoperative pain, through the use of objective hemodynamic assessment.

Methods

Study design and setting

The study took place within a prospective controlled, randomized and single-blinded format. Participants presenting to the Gynecological-Oncology Unit of the Carmel Medical Center (Haifa, Israel) were recruited (from June 2018 to May 2021).

The Integrative Oncology Program was launched at the Lin Medical Center in 2008, with the goal of providing complementary medicine therapies addressing QoL-related concerns among patients undergoing chemotherapy (Ben-Arye et al. 2012). IO treatments are provided weekly without charge to patients undergoing adjuvant, neo-adjuvant, and palliative oncology treatments. Treatments are provided by a team of 23 healthcare practitioners from a wide range of IO disciplines, all of whom have undergone training in supportive cancer care. The IO treatments are provided at two ambulatory cancer day-care centers; in a tertiary gynecological oncology referral center; in an end-of-life care (in-patient and outpatient) service; and at three remote satellite primary care clinics, as well as at a home hospice service.

Study population

Patients eligible for study inclusion were females ≥ 18 years old referred to surgery for ovarian, endometrial, or cervical cancer. Following an in-depth explanation of the study goals and proceedings, patients were required to sign an informed consent form.

Randomization to study groups

Randomization and allocation of patients to the study arms and groups are presented in Fig. 1. Recruited patients were initially randomized to either the IO intervention arm (Group A and Group B) or to the control arm, which received standard care alone (Group C). A block randomization of 9 and

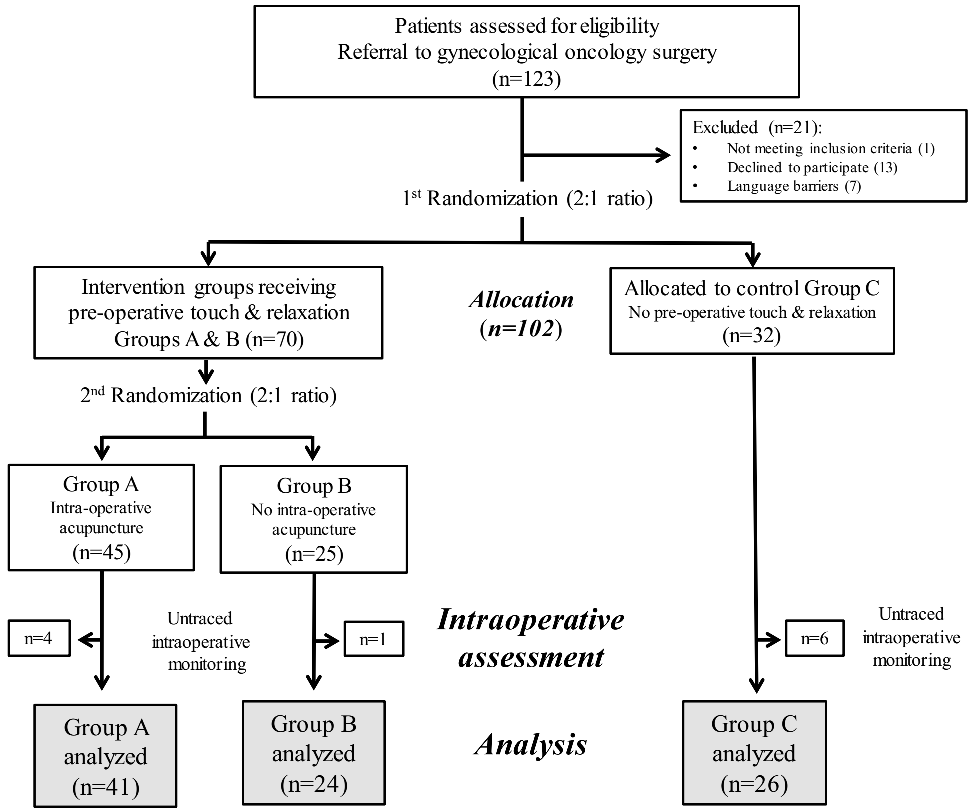

Fig. 1 Study algorithm

an allocation ratio of 2:1 in favor of the intervention group was used (Research Randomizer software; www.randomizer.org). Patients, gynecologists, anesthesiologists, nurses, and IO practitioners were blinded at this stage of randomization until the morning of the planned surgery.

On the day of surgery, patients randomized to the intervention arm were treated preoperatively with IO touch/relaxation therapies, without acupuncture. Treatment continued up until the patient was brought to the operating room, anesthetized, and intubated. By this stage of the study patients, gynecologists, anesthesiologists, nurses, and IO practitioners were unblinded as to whether the patient was in the IO intervention or control arm. A second randomization then took place, in which patients in the intervention arm were randomly allocated to intraoperative acupuncture treatment (Group A) or standard care alone (Group B). Randomization was performed using the same block of 9 randomization used in the earlier stage of the study, with a ratio of 2:1 in favor of Group A. At this stage, only patients were blinded as to their study allocation, until the 24-h follow-up assessment.

Integrative oncology treatments

The IO treatments (acupuncture and touch/relaxation modalities) were provided by practitioners who in addition to their extensive training in supportive and palliative care had also received specific training for the perioperative setting. This additional training was provided by IO-trained physicians, gynecological-oncology surgeons, anesthesiologists, and operating room nurses. Training addressed the need for ensuring effective communication throughout the perioperative intervention; maintaining safe movement during the surgery; and coordinating IO treatments (especially acupuncture) with the many activities taking place with the multi-disciplinary surgical team. Safety-related issues included maintaining the sterility of the surgical field; making sure acupuncture needles did not move or detach with movement of the patient or surgical sheets; preventing accidental acupuncture needle-pricking of the surgical and anesthesiology staff; and ensuring that no needles were lost or left in place.

To further ensure safety throughout surgery, all of the inserted needles were written down on a list by the IO practitioner (needle size and exact location). Once inserted, the handles of the acupuncture needles handles were angled parallel to the skin and then covered with a transparent adhesive tape to prevent movement and to avoid accidental needle-pricking of the surgeons, nurses, or anesthesiologists. At the end of surgery, the practitioner was required to check off each needle used on the list as it was removed, with an inventory of the needles then taken.

A number of acupuncture points were selected based on their effectiveness, as shown in prior research in the reduction of pain in the IO setting (Ben-Arye et al. 2021):

Liver-3, *Taichong*; Large-Intestine 4, *Hegu*; Stomach-36, *Zusanli*; Pericard-6, *Neiguan*; Spleen-6, *Sanyinjiao*; *Yin tang;* EX-HN 1, *Sishencong*; as well as “battlefield” ear acupuncture points (Baldawi et al. 2022). When acupuncture points were not accessible due to restrictions of the surgery or anesthesia, acupressure was applied until the insertion of the acupuncture needle was possible.

Anesthesia protocol and monitoring

All patients received standard anesthetic care, with monitoring of their electrocardiogram (ECG), noninvasive blood pressure, end title CO_2, $Sa0_2$, and temperature; with invasive blood pressure and bispectral index (BIS) monitoring used for depth of anesthesia. Anesthesia was induced with propofol 3 (mg/kg) and fentanyl (2 mcg/kg), with rocuronium (0.6 mg/kg) given to facilitate tracheal intubation; and isoflurane (1 MAC) and O_2 (at a mean of 50%) throughout the surgery. For signs indicating insufficient analgesia, such as an increase in mean arterial pressure (MAP) or heart rate (HR) of > 20%, an additional dose of fentanyl (1 mcg/kg) was administered every 10 min until full anesthesia was reached. Intravenous paracetamol (1 gr) was given 30 min before the end of the operation. Minute ventilation was controlled and adjusted to keep the end tidal CO_2 at around 40 mmHg. For laparoscopic surgery, intra-abdominal CO_2 pressure was maintained at a maximum of 15 mmHg.

During postoperative recovery, a visual analogue scale (VAS) was used to assess pain severity at rest and upon coughing (at 30 min and at 1, 2, 6 and 24 h). The location of pain (visceral, abdominal wall/parietal, or shoulder pain) was noted as well. IV morphine (0.5 mg/kg) was administered when the VAS score exceeded 5. Additional doses of morphine (0.25 mg/kg) were given until the VAS score was reduced to < 5; IV dipyrone (1 g) or tramadol (100 mg) for pain of < 4 after 10 min. For cases of postoperative chills or shivering, IV pethidine (15 mg) was administered, with nausea and vomiting treated with IV ondansetron (4 mg). Postoperative analgesic drug usage was recorded at each of the above points in time.

All surgical proceedings were entered into a separate electronic study chart, describing the type (open laparotomy or laparoscopy) and duration of the operation; number of incisions; number of inserted trocars (≥ 10 mm); estimated loss of blood; use of pain medication (type and dosage); amount of insufflated gas used during the procedure; and adverse events. Postoperative vital signs and medications were recorded, as was the duration of stay in the post-anesthesia care unit.

Study outcome measures: anesthesia parameters

The primary study parameters measured during the intraoperative acupuncture intervention included the MAP, based on continuous arterial line monitoring, and HR. Both were used as indirect indicators of intraoperative nociception (Coulombe et al. 2021). Additional anesthesia-related variables included MAP variability (mean of MAP standard deviation, SD), BIS, and calculated Average Real Variability (ARV). The means of the MAP standard deviation and ARV were documented at 3 time periods during surgery: 10 min prior to the first surgical incision (in laparoscopic surgery, standard 5–10 mm of trocar incision); 10 min following the initial incision; and until the closing of the incision.

Statistical analysis

The study sample size was calculated using the OpenEpi program (Microsoft), which found that at least 30 patients would be needed in each arm of the study (intervention vs. control) to show a significant reduction in postoperative pain. This would allow for an alpha-error of 0.05 and beta-error of 0.2 (power 80%), identifying a 20% delta on the 10-point VAS. Statistical analyses were conducted using the IBM SPSS Statistics 24.0 program (IBM, New York, NY), with means (± standard deviation) or medians and inter-quartile range for continuous variables; and numbers and proportions for categorical variables.

For comparisons between baseline characteristics for the two arms, as well as the two intervention groups (A and B), a Chi-square test for categorical variables was used, with an ANOVA or Kruskal–Wallis test for continuous variables. Changes in anesthesia-related parameters such as MAP, from the 10 min preceding and following the initial incision, as well as those measured throughout surgery, were analyzed using a Wilcoxon sign-rank test for each. MAP was tested as an absolute value and as a mean of standard deviations from the arterial pressure variability during surgery. Kruskal–Wallis, followed by Mann–Whitney for pairwise comparisons with Bonferroni correction, were used to compare between the two intervention groups. Mann–Whitney test was used to compare changes between controls and intervention groups A & B.

BIS was analyzed by comparing mean differences between measurements at the initial incision and mean BIS values during surgery. Average real variability (ARV) was calculated from the initial incision through the entire surgery, based on the equation of Mascha et al. in which N is the number of blood pressure measurements and T is the total time from first to last BP reading (Mascha et al. 2015)

$$\text{Generalized ARV} = \frac{1}{T}\sum_{k=1}^{N-1}\left|BP_{k+1} - BP_k\right| \text{mmHg/min}.$$

Ethical considerations

The protocol of the present study was approved by the Ethics Review Board (Helsinki Committee) at the Carmel Medical Center in Haifa, Israel (CMC-18-0037) and registered at ClinicalTrials.gov (NCT03560388).

Results

Characteristics of the study groups

A total of 102 patients referred for gynecological oncology surgery during the study period consented to participate (Fig. 1). At the first randomization, patients were allocated to either the intervention ($n = 70$, Group A and Group B) or control arm of the study ($n = 32$, Group C). Following induction and intubation, the second randomization was performed, allocating patients to either intraoperative acupuncture ($n = 45$, Group A) or to standard anesthetic care alone ($n = 25$, Group B).

Table 1 presents the demographic, cancer-, anesthesiology-, and surgery-related characteristics of the cohort. All 3 groups were of similar age, primary language, and reported similar rates of past experience with complementary medicine. The groups had similar scores for American Society of Anesthesiology (ASA) surgical risk criteria; surgical-related parameters, including type of surgery performed (open laparotomy vs. laparoscopy); surgery-related complications; cancer-related parameters, including the site of the primary tumor (ovarian, uterine or cervical), and cancer recurrence; and non-cancer-related medical conditions and use of medication.

Hemodynamic and BIS during open surgery

Table 2 presents MAP values from the 10 min preceding and following the initial incision. MAP was significantly elevated within Group A (intraoperative acupuncture, $p = 0.005$) and Group C (controls, $p = 0.021$). However, MAP and HR changes were more pronounced in group A when compared to group B (MAP, $p = 0.052$; HR, $p = 0.037$). In contrast, no significant changes in MAP were observed in Group A from the first 10 min after the initial incision to the end of surgery (Table 3, Fig. 2). Between-group analysis found that Group A had stable MAP measurements throughout surgery, as opposed to elevated MAP observed in group B ($p = 0.026$) and Group C ($p = 0.025$). In addition, higher variability of mean MAP values, measured by the mean of MAP standard deviations, was recorded within Group B ($p = 0.023$) and Group C ($p = 0.036$), but not in Group A. HR was also significantly decreased throughout the surgery in group A, in contrast to elevated HR observed in group B ($p = 0.029$).

Table 3 presents the reduction in BIS measurements which, in addition to the anesthesia-related outcomes, were most significant in Group A when comparing mean BIS changes during the 10 min following the initial incision and throughout surgery (vs. Group C; $p = 0.024$). At the same time, the calculated average real variability did not differ between the groups.

Hemodynamics and BIS during laparoscopic surgery

MAP significantly increased in all groups during laparoscopic surgery, when comparing the 10 min preceding and following the initial incision (Table 2). The mean of MAP standard deviations was significantly elevated only in Groups A and B, reflecting a greater MAP variability. Unlike with open laparotomy, significantly elevated MAP during laparoscopic surgery was evident only in Group A ($p = 0.026$) when comparing the first 10 min following the initial incision and during the rest of surgery (Table 3). In this comparison, a decrease in the mean of MAP standard deviations was significant only within group B ($p = 0.047$). For ARV, calculations during laparoscopic surgery were significantly higher in Group B when compared to Group A ($p = 0.009$) and Group C ($p = 0.009$). No significant changes in BIS were observed during laparoscopic surgery, though a trend for reduced BIS was noted for Group C when compared with Group A ($p = 0.064$).

Use of analgesic medications

Table 4 presents the use of analgesic medications during surgery and in post-anesthesia care, comparing the three study groups in both open and laparoscopic surgical settings. No significant differences were found between groups for the dosages of fentanyl, midazolam, morphine, paracetamol, or dipyrone.

Adverse events

No major adverse events attributed to the IO treatments, including intraoperative acupuncture, were reported in either of the study intervention groups. At the same time, the insertion of acupuncture needles during surgery which lasted far longer than with usual acupuncture treatment (i.e., for a few hours, as opposed to 30–45 min) frequently required that more force be used during removal of needles. This was not the case, however, for needles inserted into acupuncture points on the

Table 1 Compared characteristics of patients in the three study groups

	Group A Acupuncture & touch-relax $n=41$	Group B Touch-relax only $n=24$	Group C Control $n=26$	*P* values
Age Mean ± SD (median)	63.9 ± 12.5	60.3 ± 12.1	63.4 ± 11.9	$P=0.503$
Primary language				
Hebrew	35 (85.4)	21 (87.5)	22 (84.6)	$P=0.130$
Arab	4 (9.8)	0	4 (15.4)	
Russian	2 (4.9)	3 (12.5)	0	
Prior complementary medicine use: yes	17 (42.5)	8 (33.3)	10 (41.7)	$P=0.712$
Primary cancer site:				
Ovarian	8 (19.5)	5 (20.8)	7 (26.9)	$P = 0.792$
Endometrial	16 (39.0)	12 (50.0)	12 (46.2)	
Cervical	6 (14.6)	2 (8.3)	4 (15.4)	
Other	11 (26.8)	5 (20.8)	3 (11.5)	
Cancer recurrence: yes	3 (7.5)	1 (4.2)	4 (15.4)	$P=0.403$
Cancer metastasis: yes	6 (15.0)	2 (8.3)	6 (23.1)	$P=0.375$
Background diagnosis				
Hypertension	16 (39.0)	10 (41.7)	7 (28.0)	$P = 0.558$
Diabetes	6 (14.6)	4 (16.7)	5 (20.0)	$P = 0.934$
Cardiovascular	2 (4.9)	0	2 (8.0)	$P = 0.577$
Medications				
Chronic drug treatment	27 (67.5)	14 (58.3)	16 (64.0)	$P = 0.761$
Insomnia	0	1 (4.2)	2 (8.3)	$P = 0.249$
Psychiatric	1 (2.6)	2 (8.3)	5(20.8)	$P = 0.057$
Analgesics	1 (2.6)	0	1 (4.2)	$P > 0.99$
ASA score*	2.02 ± 0.61 2 (2; 2)	1.83 ± 0.48 2 (2; 2)	2.04 ± 0.66 2 (2, 2)	0.407
First operation: yes	11(26.8)	6 (25.0)	10 (38.5)	$P=0.492$
Surgery setting				
Laparoscopic (vs. open)	26 (63.4)	10 (41.7)	14 (53.8)	$P=0.233$
Surgical complications: yes	3 (7.5)	2 (8.7)	3 (11.5)	$P=0.894$

The percentages are provided for only those responding to each question

American Society of Anesthesiology (ASA) score is a categorization of a patient's physiological status with the aiming at predicting operative risk ranging from 0 (normal) to 5 (high morbidity)

Group A includes intraoperative acupuncture and preoperative touch/relaxation techniques

Group B includes only preoperative touch/relaxation techniques

Group C includes standard care only

face and ears, for which little force was required for removal. Patients treated with acupuncture frequently reported localized and mild redness surrounding the acupuncture needles during the postoperative recovery. The discomfort was brief and localized, and rarely extended beyond the acupuncture point.

Discussion

The present study explored the impact of intraoperative acupuncture intervention on hemodynamic and other anesthesia-related parameters during open and laparoscopic gynecological oncology surgery. A significant improvement in hemodynamic and anesthesia-related parameters was observed among patients undergoing open laparotomy. As shown in Table 3, intraoperative acupuncture (from the initial incision to suturing) was associated with decreased MAP (compared with groups B and C) and HR (compared with group B), with a significant decrease in BIS (compared with Group C). At the same time, no beneficial effect was found with the intervention in patients undergoing laparoscopic surgery. The greater impact of acupuncture on MAP and HR in the acupuncture-treated group may suggest an intraoperative nociceptive effect, which in turn may have

Table 2 Anesthesia monitoring data 10 min prior and following the initial incision comparing the three study groups

Parameters	Group A Acupuncture & touch-relax $n=41$ Mean score ± SD Median (IQR)		Group B Touch-relax only $n=24$ Mean score ± SD Median (IQR)		Group C Control $n=26$ Mean score ± SD Median (IQR)		*P* values
	10 min preceding the initial incision	10 min following the initial incision	10 min preceding the initial incision	10 min following the initial incision	10 min preceding the initial incision	10 min following the initial incision	
Open surgery							
MAP—absolute value	$n=13$ 71.0 ± 10.2 68 (65; 78)	$n=13$ 86.0 ± 14.7 84 (75; 97)	$n=12$ 71.0 ± 11.7 69 (66; 79)	$n=12$ 76.0 ± 15.8 72 (66; 79)	$n=9$ 67.1 ± 4.4 67 (65; 70)	$n=9$ 80.4 ± 10.1 79 (73; 89)	$P^1=0.499$ $P^2=0.005$ $P^3=0.583$ $P^4=0.021$ $P^5=0.096$ $P^6=0.111$ $P^7=0.601$ $P^8=0.052$
Mean of MAP SDs	$n=12$ 4.7 ± 4.4 3 (1, 9)	$n=12$ 9.7 ± 9.5 6 (3; 15)	$n=12$ 4.4 ± 2.5 4 (2; 7)	$n=12$ 6.4 ± 4.1 7 (3; 10)	$n=8$ 9.7 ± 7.2 7.7 (5; 7)	$n=8$ 5.8 ± 5.6 6 (2; 9)	$P^1=0.102$ $P^2=0.182$ $P^3=0.444$ $P^4=0.327$ $P^5=0.266$ $P^6=0.238$ $P^7=0.135$ $P^8=0.671$
Heart rate	$n=15$ 72.5 ± 11.6 73 (62; 82)	$n=15$ 73.7 ± 13.5 73 (66; 83)	$n=13$ 69.6 ± 11.2 69 (60; 82)	$n=13$ 67.3 ± 13.7 67 (58; 76)	$n=12$ 69.9 ± 15.2 68 (57; 82)	$n=12$ 72.2 ± 15.6 68 (59; 87)	$P^1=0.762$ $P^2=0.307$ $P^3=0.152$ $P^4=0.378$ $P^5=0.045$ $P^6=0.030$ $P^7=0.614$ $P^8=0.037$
Laparoscopic surgery							
MAP—absolute value	$n=24$ 81.8 ± 20.7 78 (68; 82)	$N=24$ 92.6 ± 16.2 91 (80; 107)	$n=10$ 75.8 ± 11.5 78 (68; 82)	$n=10$ 96.2 ± 13.0 101 (92; 104)	$n=10$ 79.4 ± 12.3 77 (69; 91)	$n=10$ 95.6 ± 13.7 96 (82; 110)	$P^1=0.880$ $P^2=0.036$ $P^3=0.017$ $P^4=0.014$ $P^5=0.687$ $P^6=0.579$ $P^7=0.809$ $P^8=0.423$
Mean of MAP SDs	$n=23$ 9.7 ± 14.4 4.9 (2, 12)	$n=23$ 19.8 ± 17.3 16.6 (5; 33.2)	$n=10$ 9.0 ± 5.3 7 (5; 14)	$n=10$ 30.8 ± 17.5 30 (18; 41)	$n=9$ 11.1 ± 4.1 12.7 (7.5; 13)	$n=9$ 17.9 ± 13.2 13.4 (7.; 26)	$P^1=0.080$ $P^2=0.023$ $P^3=0.013$ $P^4=0.172$ $P^5=0.179$ $P^6=0.053$ $P^7=0.409$ $P^8=0.237$
Heart rate	$n=26$ 69.9 ± 10.2 70 (62; 77)	$n=26$ 70.5 ± 8.7 71 (63; 79)	$n=10$ 65.3 ± 11.5 61 (58; 73)	$n=10$ 67.3 ± 13.2 65 (60; 72)	$n=13$ 69.7 ± 14.2 73 (54; 81)	$n=13$ 69.4 ± 14.3 67 (57; 76)	$P^1=0.442$ $P^2=0.844$ $P^3=0.331$ $P^4=0.919$ $P^5=0.724$ $P^6=0.446$ $P^7=0.872$ $P^8=0.520$

Table 2 (continued)

IQR Interquartile Range MAP, Mean arterial pressure

ARV Average real variability from initial incision through the entire surgery

P values are presented concerning the following comparisons between the groups:

P^1 = compared three group baseline scores during the 10 min following the initial surgery incision;

P^2 = within Group A changes comparing the 10 min following the initial incision to the entire surgery duration

P^3 = within Group B changes comparing the 10 min following the initial incision to the entire surgery duration

P^4 = within Group C changes comparing the 10 min following the initial incision to the entire surgery duration

P^5 = between all 3-group changes comparing the 10 min following the initial incision to the entire surgery duration

P^6 = between Group B and Group C changes comparing the 10 min following the initial incision to the entire surgery duration

P^7 = between Group A and Group C changes comparing the 10 min following the initial incision to the entire surgery duration

P^8 = between Group A and Group B changes comparing the 10 min following the initial incision to the entire surgery duration

led to reduced postoperative pain, a finding reported in an earlier study of the study setting for Group A (Ben-Arye et al. 2012). This hypothesis needs to be further explored using more comprehensive measures of nociception, such as nociceptive levels (NOL) (Ben-Israel et al. 2013).

To the best of our knowledge, this is the first randomized-controlled trial using objective measurements to assess the effects of acupuncture in the complex surgical setting, requiring collaboration and coordination with the anesthesiology, surgery, and nursing team. The intraoperative setting presents a unique opportunity to test the effects of IO therapies, such as acupuncture. This setting allows for the blinding of patients as to their allocation of treatment; and use objective hemodynamic measures, as opposed to only subjective patient-reported outcomes. In the present study regimen, preoperative manual and mind–body therapies, which may stimulate non-specific effects, were provided to both intervention groups, with the control group receiving no IO treatment whatsoever.

The published research on the effects of acupuncture on intraoperative MAP is limited, and to the best of our knowledge, it has not examined the gynecologic oncology surgery setting. Electro-acupuncture stimulation was shown to reduce MAP in anaesthetized rats with steroid-induced polycystic ovaries (Stener-Victorin et al. 2004). However, no significant effect was found in patients receiving preoperative or intraoperative electro-acupuncture for elective sinusotomy or supratentorial craniotomy (Liu et al. 2015; Wang et al. 2014; Yu et al. 2014). Finally, a significantly lower change in MAP was observed following acupuncture needle insertion during endotracheal intubation for general anesthesia (Rahimi et al. 2019).

The impact of acupuncture on BIS, shown in the present study to be more significantly reduced with acupuncture, has been reported in an earlier study examining electro-acupuncture stimulation in patients undergoing therapeutic abortions (Cheng et al. 2010). Decreased BIS values have also been reported in patients receiving acupuncture prior to induction in surgical settings (Acar et al. 2013; Paraskeva et al. 2004; Chen et al. 2020). At the same time, elevated BIS values were found in patients treated with postoperative acupuncture in specific points directed at restoring consciousness and "eye-opening" after general anesthesia (Faiz et al. 2019).

In the present study, acupuncture significantly increased MAP during laparoscopic surgery, with no effect on HR or BIS, similar to what was shown during open laparotomy. MAP significantly increased for all three groups in this setting, from the 10 min preceding and the 10 min following the initial incision. The mean of MAP standard deviations was significantly higher in groups A and B, suggesting a greater degree of change and lesser MAP stability during the first 10 min post-incision. A similar hypertensive effect (MAP) was also apparent in the acupuncture-treated and control groups in the open laparoscopic surgery setting and at 10 min post-incision.

These findings raise the question as to the potential for acupuncture to significantly impact hemodynamics during the first 10 min preceding the initial surgical incision, as shown in Table 2. It is also unclear regarding the beneficial effect of acupuncture in the laparoscopic (vs. open laparotomy) surgery setting, in light of the associated increase in MAP variability. One explanation of this discrepancy may be that during laparoscopy, the patient is lying down in non-physiological (Trendelenburg) position which, together with the high intraperitoneal pressure from the pneumo-peritoneum, may increase sympathetic cardiac activity (Sato et al. 2000). In addition, it has been shown that acupuncture may alter heart-rate variability by increasing parasympathetic tone (Hamvas et al. 2023; Chung et al. 2014). In a study of healthcare providers working in isolated COVID-19 departments, acupuncture was shown to impact heart-rate variability through both increased parasympathetic and decreased sympathetic activity (Vagedes et al. 2023). The use of nociceptive monitoring, such as NOL and heart-rate variability assessment, may shed light on these and other questions regarding the findings of the present research in both the open and laparoscopic surgery settings.

Table 3 Anesthesia monitoring changes from initial incision up to suture closing comparing the three study groups

Parameters	Group A Acupuncture & touch-relax *n* = 41 Mean score ± SD Median (IQR)		Group B Touch-relax only *n* = 24 Mean score ± SD Median (IQR)		Group C Control *n* = 26 Mean score ± SD Median (IQR)		*P* values
	10 min following the initial incision	Entire surgery¥	10 min following the initial incision	Entire surgery¥	10 min following the initial incision	Entire surgery¥	
Open surgery							
BIS	*n* = 14 40.3 ± 9.3 39 (34, 47)	*n* = 14 37.3 ± 5.7 37 (33, 43)	*N* = 14 40.3 ± 6.4 40 (35; 45)	*N* = 14 39.2 ± 5.3 39 (36; 42)	*N* = 8 36.0 ± 10.3 37 (27; 46)	*N* = 8 40.8 ± 6.6 40 (35; 46)	$P^1=0.499$ $P^2=0.109$ $P^3=0.397$ $P^4=0.069$ $P^5=0.069$ $P^6=0.082$ $P^7=0.024$* $P^7=0.297^{\mu}$ $P^8=0.603$
MAP—absolute value	*n* = 13 85.7 ± 14.7 84 (75; 97)	*n* = 13 85.5 ± 10.4 82 (78; 91)	*n* = 12 76.0 ± 15.8 73 (66; 79)	*n* = 12 89 ± 20.5 85 (78; 90)	*n* = 9 80.5 ± 10.1 79 (73; 89)	*n* = 9 89.5 ± 11.7 88 (85; 96)	$P^1=0.083$ $P^2=0.917$ $P^3=0.019$ $P^4=0.015$ $P^5=0.026$ $P^6=0.651$ $P^7=0.025$ $P^8=0.026$
Mean of MAP SDs	*n* = 12 9.7 ± 9.5 6 (3; 15)	*n* = 12 12.0 ± 5.1 11 (8; 16)	*n* = 12 6.4 ± 4.1 7 (3; 10)	*n* = 12 13.8 ± 11.8 11 (9, 15)	*n* = 8 5.8 ± 4.5 6 (2; 9)	*n* = 8 14.4 ± 10.2 10 (8; 20)	$P^1=0.685$ $P^2=0.209$ $P^3=0.023$ $P^4=0.036$ $P^5=0.539$ $P^6=0.624$ $P^7=0.270$ $P^8=0.630$
Heart rate	*n* = 15 73.7 ± 13.5 73 (66; 83)	*N* = 15 69.6 ± 9.6 70 (64; 75)	*n* = 13 67.3 ± 13.7 6 (58; 76)	*n* = 13 72.2 ± 13.8 68 (61; 80)	*n* = 12 72.2 ± 15.6 68 (59; 87)	*n* = 12 72.4 ± 15.0 68 (61; 84)	$P^1=0.392$ $P^2=0.156$ $P^3=0.023$ $P^4=0.272$ $P^5=0.066$ $P^6=0.247$ $P^7=0.200$ $P^8=0.029$
ARV	*n* = 13 1.66 ± 0.64 1.6(1.1–2.1)		*n* = 12 1.62 ± 0.74 1.5 (1.2–2.1)		*n* = 9 1.84 ± 0.87 1.9 (1.2–2.3)		$P^6=0.508$ $P^7=0.695$ $P^8=0.769$
Laparoscopic surgery							
BIS	*n* = 23 35.9 ± 9.3 35 (31, 43)	*n* = 23 36.2 ± 6.1 36 (32, 39)	*n* = 9 38.5 ± 5.2 40 (34; 42)	*n* = 9 39.7 ± 7.7 39 (34; 43)	*n* = 9 43.5 ± 14.7 43 (31; 58)	*n* = 9 39.2 ± 9.5 42 (34; 45)	$P^1=0.366$ $P^2=0.637$ $P^3=0.594$ $P^4=0.594$ $P^5=0.757$ $P^6=0.666$ $P^7=0.805$* $P^7=0.064^{\mu}$ $P^8=0.483$

Table 3 (continued)

Parameters	Group A Acupuncture & touch-relax $n=41$ Mean score ± SD Median (IQR)		Group B Touch-relax only $n=24$ Mean score ± SD Median (IQR)		Group C Control $n=26$ Mean score ± SD Median (IQR)		P values
	10 min following the initial incision	Entire surgery¥	10 min following the initial incision	Entire surgery¥	10 min following the initial incision	Entire surgery¥	
MAP—absolute value	$n=24$ 92.6 ± 16.2 91 (80; 107)	$n=24$ 100.4 ± 13.1 103 (90; 107)	$n=10$ 96.2 ± 13.0 101 (92; 104)	$n=10$ 98.8 ± 9.1 97 (93; 105)	$n=10$ 95.6 ± 13.7 96 (82; 110)	$n=10$ 95.0 ± 12.2 101 (86; 104)	$P^1=0.760$ $P^2=0.026$ $P^3=0.386$ $P^4=0.878$ $P^5=0.183$ $P^6=0.684$ $P^7=0.118$ $P^8=0.183$
Mean of MAP SDs	$n=23$ 19.8 ± 17.3 16.6 (5; 33.2)	$n=23$ 12.9 ± 4.0 13 (10; 16)	$n=10$ 30.8 ± 17.5 30 (18; 41)	$n=10$ 15.3 ± 9.0 14 (11, 16)	$n=9$ 17.9 ± 13.2 13.4 (7; 26)	$n=9$ 9.9 ± 2.0 10 (8; 12)	$P^1=0.168$ $P^2=0.144$ $P^3=0.047$ $P^4=0.139$ $P^5=0.417$ $P^6=0.356$ $P^7=0.651$ $P^8=0.237$
Heart rate	$n=26$ 70.5 ± 8.7 71 (63; 79)	$n=26$ 70.6 ± 11.4 67 (63; 75)	$n=10$ 67.3 ± 13.2 65 (60; 72)	$n=10$ 67.1 ± 13.1 64 (59; 74)	$n=13$ 69.4 ± 14.3 67 (57; 76)	$n=13$ 70.6 ± 10.8 73 (66; 76)	$P^1=0.494$ $P^2=0.929$ $P^3=0.646$ $P^4=0.422$ $P^5=0.746$ $P^6=0.313$ $P^7=0.803$ $P^8=0.768$
ARV	$n=24$ 1.9 ± 0.59 1.8 (1.5–2.1)		$n=10$ 2.5 ± 0.72 2.3 (2.0–3.0)		$n=10$ 1.66 ± 0.49 1.4 (1.3–2.2)		$P^6=0.009$ $P^7=0.238$ $P^8=0.009$

IQR Interquartile Range, *BIS* Bispectral index, *MAP* Mean Arterial Pressure

ARV, Average Real Variability from initial incision through the entire surgery

¥Entire surgery: from 10 min following the initial incision to the wound closure

*Compared BIS mean differences between initial incision and the entire surgery

µCompared BIS means within the entire surgery

P values are presented concerning the following comparisons between the groups:

P^1 = compared three group baseline scores during the 10 min following the initial surgery incision;

P^2 = within Group A changes comparing the 10 min following the initial incision to the entire surgery duration

P^3 = within Group B changes comparing the 10 min following the initial incision to the entire surgery duration

P^4 = within Group C changes comparing the 10 min following the initial incision to the entire surgery duration

P^5 = between all 3-group changes comparing the 10 min following the initial incision to the entire surgery duration

P^6 = between Group B and Group C changes comparing the 10 min following the initial incision to the entire surgery duration

P^7 = between Group A and Group C changes comparing the 10 min following the initial incision to the entire surgery duration

P^8 = between Group A and Group B changes comparing the 10 min following the initial incision to the entire surgery duration

The present study has a number of limitations, most significantly the absence of intraoperative nociceptive measurements, in addition to hemodynamic monitoring. These could include measurements such as skin-associated responses (Stomberg et al. 2001), somatosensory-evoked potentials (Zanatta et al. 2011), heart-rate variability (Analgesia Nociception Index); as well as photoplethysmography, skin conductance, and temperature-related Nociception Level

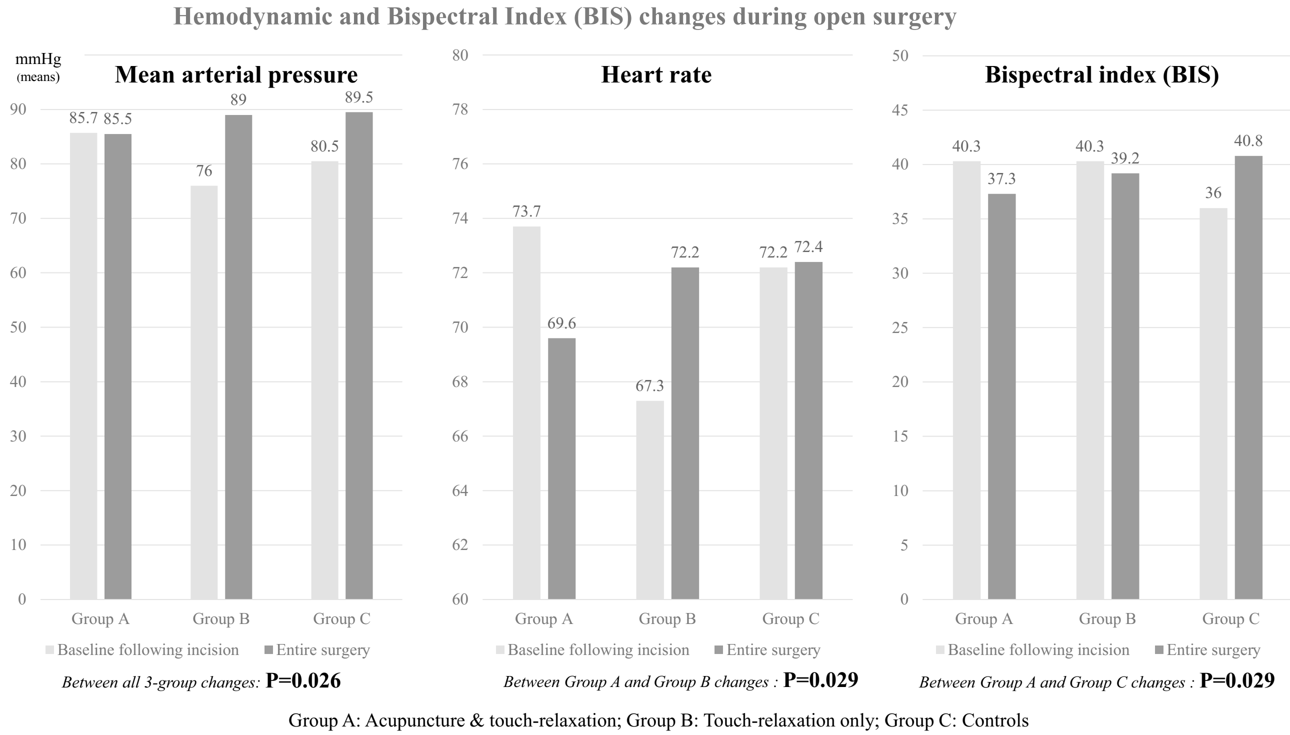

Fig. 2 Hemodynamic and Bispectral Index changes during open surgery

Table 4 Analgesic use throughout the surgery and in post-anesthesia care unit comparing the three study groups

Parameters	Open surgery				Laparoscopic surgery			
	Group A Acupuncture & touch-relax	Group B Touch-relax only	Group C Control	*P* values	Group A Acupuncture & touch-relax	Group B Touch-relax only	Group C Control	*P* values
	During surgery							
Fentanyl mcg/kg patient weight	$n=10$ 4.0 ± 2.2 3 (3.4)	$n=9$ 3.4 ± 1.2 3 (3.4)	$n=7$ 3.4 ± 1.8 3 (3.4)	$P^1=0.885$ $P^2>0.99$ $P^3=0.813$ $P^4=0.720$	$n=13$ 3.8 ± 1.4 3 (3.5)	$n=4$ 3.8 ± 1.5 3 (3–5.3)	$n=12$ 3.4 ± 0.99 3 (3.3)	$P^1=0.701$ $P^2=0.770$ $P^3=0.538$ $P^4=0.956$
Midazolam mg	$n=6$ 1.7 ± 0.51 2 (1; 2)	$n=6$ 1.7 ± 0.51 2 (1; 2)	$n=7$ 1.5 ± 0.5 1.5 (1; 2)	$P^1>0.99$ $P^2=0.628$ $P^3=0.628$ $P^4>0.99$	$n=11$ 1.5 ± 0.68 1 (1; 2)	$n=7$ 1.8 ± 1.5 1 (1; 2)	$n=4$ 2 ± 1.4 1.5 (1; 3.5)	$P^1=0.836$ $P^2=0.788$ $P^3=0.571$ $P^4=0.860$
Post-anesthesia care unit								
Morphine mg	$n=10$ 4 ± 2.2 3 (3, 4)	$n=9$ 3.4 ± 1.2 3 (3; 4)	$n=7$ 3.4 ± 1.8 3 (3, 4)	$P^1=0.598$ $P^2>0.99$ $P^3=0.813$ $P^4=0.720$	$n=13$ 3.8 ± 14 3 (3, 5)	$n=4$ 3.8 ± 1.5 3 (3; 5.25)	$n=12$ 3.4 ± 0.99 3 (3, 3)	$P^1=0.888$ $P^2=0.770$ $P^3=0.538$ $P^4=0.956$
Paracetamol *N* (%)	1 (6.3)	1 (7.1)	1 (7.1)	$p>0.99$	3 (10.3)	1 (9.1)	2 (11.1)	$p>0.99$
Dipyrone *N* (%)	4 (25.0)	2 (14.3)	3 (21.4)	$P=0.895$	5 (17.2)	4 (36.4)	4 (22.2)	$P=0.456$

P values are presented concerning the following comparisons between the groups:

P^1 = between all 3 groups;

P^2 = between Group B and Group C

P^3 = between Group A and Group C

P^4 = between Group A and Group B

Index (Shahiri et al. 2021; Edry et al. 2016). In addition, the statistical study power calculation was based on a clinical VAS pain scale, rather than intraoperative hemodynamic or nociceptive measurements. Other study limitations include the lack of intraoperative blinding of the medical staff (surgeons, anesthesiologists, and nurses) and IO practitioners. Finally, the fact that the study took place in a single medical center in Israel precludes reaching any conclusions regarding the generalizability of the findings.

In conclusion, the present study is, to the best of our knowledge, the first to examine the impact of intraoperative acupuncture as part of an IO intervention in a gynecological oncology surgical setting. The findings suggest that intraoperative acupuncture—from the initial incision to the closing suture—may stabilize MAP and HR, while lowering BIS in open laparotomy. This in contrast with an elevated MAP in patients undergoing laparoscopy. Further multicenter studies are needed to verify these results and their generalizability, employing more comprehensive methods to assess intraoperative nociception, and to explore the implications of the IO intervention on clinical and surgery-related outcomes.

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Author contributions EBA, IH, YS, OG, GG, and OL organized the trial and collected the data analyzed this study. EBA, MG, NS, OG, ES, and OL planned the study. EBA, NS, IH, and NS carried out the analysis and wrote a draft manuscript. All authors reviewed the manuscript.

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Data availability All relevant raw data, will be freely available to any researcher wishing to use them for non-commercial purposes, without breaching participant confidentiality.

Declarations

Conflict of interest Eran Ben-Arye, Irena Hirsh, Yakir Segev, Michael Grach, Noah Samuels, Viraj Master, Arie Eden, Nili Stein, Ludmila Ostrovsky, Orit Gressel, Galit Galil1, Meirav Schmidt, Elad Schiff, and Ofer Lavie declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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