Optimal timing of parasternal intercostal nerve block application (pre-incisional versus post-incisional) for acute pain management in cardiac surgery; a randomized double-blinded clinical trial

Samar Rafik Amin, Mona Sobhy Emara

Department of Anesthesia and ICU, Faculty of Medicine, Benha University, Benha, Egypt

Correspondence to Samar Rafik Amin, MD, 7 Ahmed Maher street, Benha, AlQaluobia 13512, Egypt. Mobile: +2 01287793991; fax: +20 (2) 13227518; e-mail: samar.rafik@gmail.com

Received: 23 February 2023
Revised: 17 May 2023
Accepted: 21 May 2023
Published: 17 August 2023

The Egyptian Journal of Cardiothoracic Anesthesia 2023, 17:28–35

Background
In patients undergoing cardiac operations, parasternal intercostal nerve block (PSIB) has been suggested to enhance pain management and lower opioids consumption. However, inadequate literature has discussed its effectiveness as a pre-emptive analgesic approach. This trial was designed to investigate the optimal timing to perform the block pre- or post-surgical incision.
Methods
This prospective study enrolled 51 patients, aged 18–70 years, with ASA status II/III, who underwent on-pump cardiac surgery. Participants were allocated to two groups randomly; Group-A received ultrasound-guided PSIB pre-incisional, while in Group-B, the surgeon performed the block under direct vision. Ten bilateral injections of four milliliters each containing bupivacaine (0.25%) were given (40 ml total volume). The study primary outcome was the amount of morphine consumed within postoperative 24 h. The secondary measures included fentanyl utilization and hemodynamic swings during surgery, as well as postoperative pain scores, rescue analgesic doses, adverse events, extubation time, ICU and hospital stay durations, and patients' satisfaction.
Results
The pre-incisional PSIB demonstrated significant decrease in intraoperative fentanyl utilization (893.85±113.39 ug vs. 982±129.81 ug, P =0.01) and more stabilization of hemodynamics at skin incision and sternal retraction time-points, compared to postincisional group. Otherwise, no significant differences were noted regarding the total postoperative morphine consumption (28.54±17.17 mg vs. 27.92±15.52 mg), pain scores, rescue analgesic demand, extubation time, length of ICU stay, hospitalization duration in both groups.
Conclusion
Pre-incisional and post-incisional PSIB presented comparable pain profile in the early postoperative period after open heart surgeries. But pre-emptive application of PSIB showed better control of intraoperative hemodynamics and less fentanyl utilization.

Keywords:
heart surgery, morphine, nerve block, pain, postoperative

Egypt J Cardiothorac Anesth 17:28–35

1687-9090

Introduction

Patients undergoing cardiac surgery frequently describe significant post-surgical pain arising from the median sternotomy. Inadequately managed pain may activate the sympathetic nervous system, which increases the risk of cardiac dysrhythmia, myocardial ischemia, and respiratory complications. Also, uncontrolled pain increases the risk of immuno-suppression, infection, poor wound healing, and development of chronic pains, which have a negative influence on the patient quality of life and require high social costs [1]. Although opioids are the most popular analgesic option for managing postoperative cardiac pain, using opioids frequently has considerable adverse events such as; drowsiness, depression of respiration, postoperative nausea and vomiting, and delayed bowl activity [2]. According to enhanced recovery after surgery protocols, a growing concept to use multimodal opioid-sparing techniques has been advocated to control pain. The synergistic and/or additive effects, produced by combining multiple analgesics, permit lower opioid doses use in surgical patients [3].

Previous literature has documented the role of thoracic epidural and thoracic paravertebral blocks as efficient

regional analgesics that can reduce postoperative mortality and morbidity in open-heart surgeries. But these invasive procedures come with a significant risk of hematoma formation in patients using anticoagulants, Dural puncture, severe hypotension, and increased failure rates [4].

To avoid these undesirable effects, many inter-facial plane blocks have been developed as easy, efficient, and low-risk interventions for analgesia of the thoracic wall. Para-sternal intercostal nerve block (PSIB) has been suggested to control pain in antero-medial chest wall. It involves local anesthetic (LA) infiltration in the area around the sternum, where the anterior branches of intercostal nerves, the primary source of poststernotomy pain, are located [5]. Conventionally, PSIB has been performed in cardiac surgery as a single-shot LA infiltration in every inter-costal space under the surgeon direct vision prior sternal closure [6]. Later, Ultrasound-guided approach was suggested by Thomas *et al.* to supply PSIB in a sternal fracture case [7]. Subsequent studies confirmed the reliability of ultrasound-guided PSIB as a safe and efficient approach [5].

The idea of pre-emptive analgesia dates back over a century, when it was hypothesized that impeding noxious signals prior surgical trauma may have a neuroprotective effect against post-surgical pain, which is today known as central desensitization. It is now understood that post-surgical pain can be amplified if central or peripheral sensitization develops following surgical incision [8]. So, in the short-term, reducing postsurgical or traumatic pain and accelerating recovery may be possible by delaying the development of central processing with analgesic therapy. Long-term advantages include a decrease in chronic pain occurrence and an enhancement in the patients' quality of recovery and level of satisfaction [9].

Although preemptive analgesia is a valid concept for reducing postinjury pain, few clinical trials have investigated the impact of preemptive peripheral nerve block applications for managing postoperative pain [9]. The study objective was to identify the effectiveness of performing ultrasound-guided para-sternal intercostal nerve block by the anesthetist before skin incision versus doing the same block by the surgeon under direct vision before sternal closure. The study variables were perioperative pain scores and opioids requirements up to 24 h postoperatively.

Patients and methods

After gaining our institutional ethics committee permission with study number (RC.1-3-2022) and collecting the signed informed consents from the participants, this prospective randomized double-blinded trial was performed at a university hospital from March 2022 to December 2022, in agreement with the Helsinki Declaration_2013 principles. Also, the trial was registered prospectively in the clinicaltrials.gov and gained a specific identification number (NCT05363540).

In this study, fifty-one patients aged 18–70 years, of both genders, with an American Society of Anesthesiologists (ASA) physical status II–III who secluded for elective on-pump cardiac operations involving median sternotomy under general anesthetics were involved. On the other hand, patients with chronic liver dysfunction, hematological disease, chronic renal failure, impaired cognitive function (inability to judge visual pain scale), allergies to local anesthetic medications, or opioid addiction issues, were excluded from the trial. Also, patients who needed preoperative inotropes, an intra-aortic balloon pump, mechanical ventilation, or underwent previous heart surgery were excluded from participation. Lastly, if the CPB time extended more than 150 min or the intubation time was greater than 12hrs postoperative, the participant was omitted from the study.

A random table list, generated by computer, was used to divide the participants into two groups randomly, and sealed opaque envelopes were employed to obscure the nature of the intervention. A nurse who was not engaged in the trial asked each patient to select a sealed envelope containing a participation number and the envelop was unsealed just before anesthesia induction. An experienced anesthesiologist, who was not participating in the intra-operative management of the patient, conducted the block to guarantee the quality and consistency of the blocks. Also, the same surgical team performed all operations, and the same anesthetic and surgical techniques were applied. For blinding, neither the patient nor the anesthesia resident who followed the patients and documented data after surgery knew to which group patient belonged.

In the pre-anesthetic clinic, patients were evaluated for eligibility and signed the informed consents. Patients were instructed regarding patient-controlled analgesia (PCA) devise and the visual analogue scale (VAS); A 10-cm handwritten line representing a continuous

spectrum between 'zero= no pain' and 'ten= worst pain' was used to record VAS values.

According to our institute's standard care protocol for cardiac anesthesia, all patients received famotidine (20 mg) and oral diazepam (0.2 mg/kg) as pre-medications in the night before the surgery. In the operation room, an 18-gauge intravenous (IV) cannula and a 20-gauge radial artery catheter were placed. Following the application of monitoring devices (pulse oximetry, invasive arterial pressures, electrocardiography, and capnography), anesthesia was initiated using midazolam (0.1 mg/kg), fentanyl (2–5 μg/kg), propofol (1.0 mg/kg), and rocuronium (1.0 mg/kg) to facilitate endo-tracheal intubation. To deliver inotropes and vasodilators and monitor central venous pressure, a triple-lumen central venous catheter was placed.

Maintenance of anesthesia was achieved by isoflurane (0.5% to 1.5%) with oxygen and air mixture, and fentanyl infusion (5–10 μg/kg/h). Mean arterial pressure (MAP) and heart rate (HR) values were preserved within (20%) of the baseline. Central temperature, central venous pressure, and urinary output were monitored, and serial arterial blood gases were investigated. Intraoperative Hypertension or hypotension were managed by boluses of Propofol/fentanyl/nitroglycerine or phenylephrine/norepinephrine, respectively. At the conclusion of the procedure, patients received (0.05 mg/kg) morphine IV before being transported to the intensive care unit (ICU).

Pre-incisional parasternal block (**Group-A**) was performed under ultrasound guidance by an experienced anesthesiologist. The intubated patient was in the supine position, and the injection site was prepared before the surgical procedure started. Linear ultrasound probe (General Electric 'GE' LOGIQ_P5) was positioned between the second and sixth intercostal spaces, 2–3 cm lateral to the midline. To inject LA into the fascial plane between pectoralis major muscle and external intercostal muscles, the block needle was advanced in a caudo-cranial direction till the tip was positioned on the costal surface to prevent piercing the pleura. The parasternal areas between the second and sixth intercostal spaces were bilaterally injected with four milliliters of bupivacaine (0.25%) for a total of ten injections (40 ml volume).

Post-incisional parasternal block (**Group-B**) was performed by the surgeon at the surgery end just before suturing the sternum. Similar sites and volumes of bupivacaine (0.25%) were injected in the parasternal spaces under the cardiac surgeon direct vision. Moreover, 4 ml of bupivacaine (0.25%) were administrated in the place of the mediastinal drain tube to all patients of both groups.

Patients were moved to ICU following the sternal closure, linked to a mechanical ventilator, and given a midazolam (0.5 mg/h) infusion to keep them asleep until extubation time. To maintain the MAP between 70 and 90 mmHg; inotropes, vasodilators, and vasoconstrictors were given. In accordance with standard ICU analgesic regimen, paracetamol (1 gm/8 h) was administered along with the PCA pump that was designed to administer a 2 mg bolus of morphine with a 10-minute lockout interval and a 40 mg maximum dose over four hours. Patients who exceeded the maximum lockout dose of PCA during the 4-hour window and whose VAS remained above 3 received rescue analgesia with IV tramadol (1 mg/kg).

The study primary outcome included the amount of consumed morphine within the first 24 h after surgery. The measured secondary outcomes included Intra-operative total fentanyl utilization (starting from induction of anesthesia till the start of cardio-pulmonary bypass [CPB]), hemodynamic variables at different stress-points (at baseline, skin incision, sternotomy, sternum retractor placement, and sternal closure). Postoperatively, extubation time (The time from ICU admission till removal of endo-tracheal tube), VAS scores at eye-opening, 6th, 12th, 18th, and 24th hour postoperative at rest and during cough, rescue analgesic demand (time of 1st request and number of doses), adverse effects (LA systemic toxicity, allergic reaction, hemodynamic instability, intravascular inject and pleural puncture), length of ICU stay, hospitalization duration, and patient satisfaction with pain control were noted. A 5-point Likert scale was used to evaluate the patient's level of satisfaction, with 1 denoting 'extremely unsatisfied,' 2 'unsatisfied,' 3 'unsure,' 4 'satisfied,' and 5 'very satisfied'.

Statistical analysis

The measured data were gathered, checked, edited, and finally analyzed via SPSS version_25 (IBM, Armonk, NY, USA). The normality of quantitative data was tested using the Shapiro-Wilk test and the Q-Q plots. Mean (SD) and median (interquartile range) were used to display quantitative data. While percentages and numbers were used to display the qualitative data. To compare quantitative variables between two

independent groups, an (unpaired t-test) was employed. To assess qualitative variables between two groups, the (Chi-square test) was performed. Statistical significance was defined as a *P*-value of 0.05 or less.

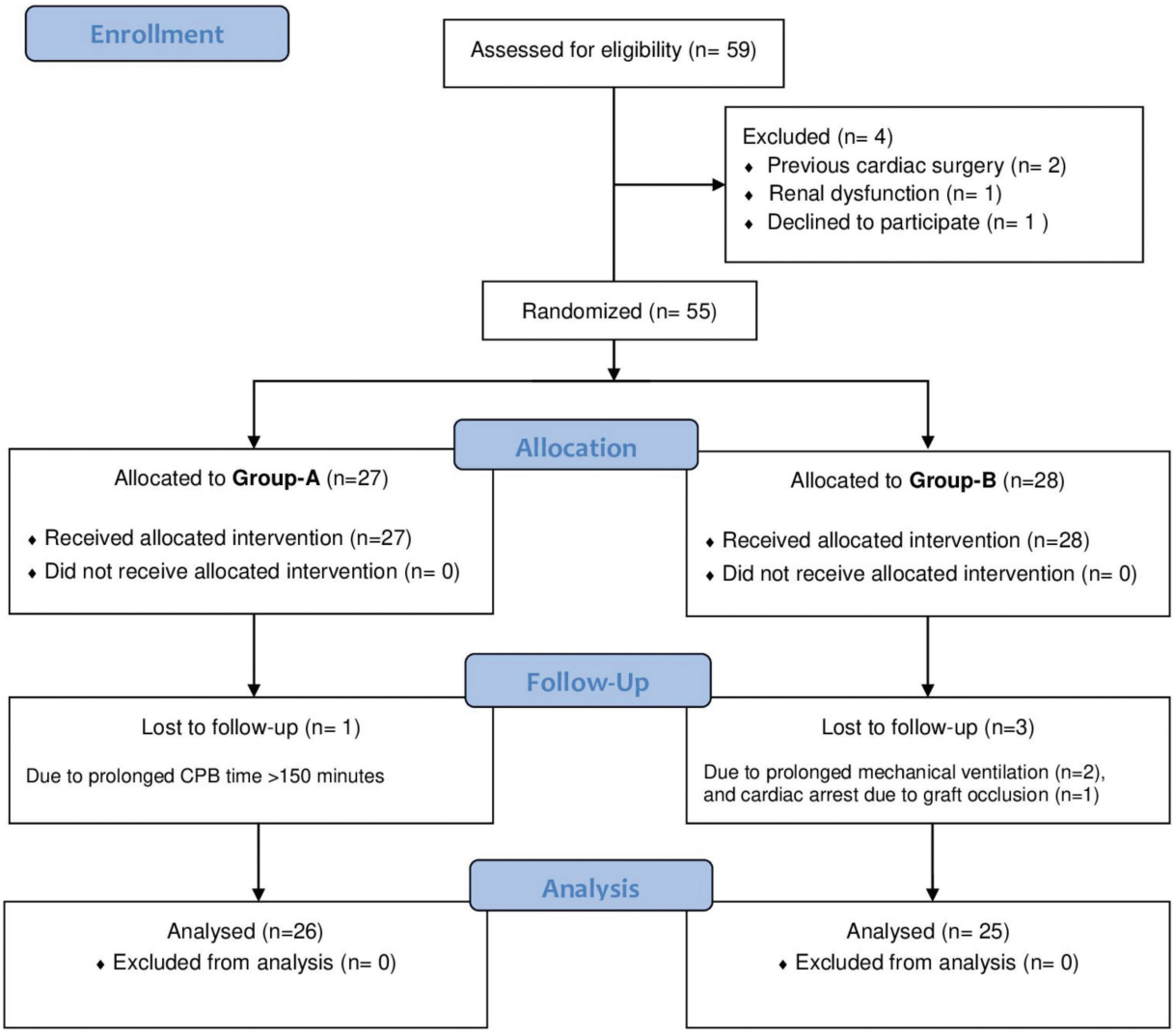
The sample size estimation used data from our pilot trial, which included 10 patients in each group. According to preliminary statistics, both the pre-incisional and post-incisional PSIB groups used a total of 20.9 mg and 7.5 mg of PCA morphine, respectively. A type-1 error of 0.05 and a power of 0.80 were used in the calculations by G-Power (Heinrich-Heine-Universität Düsseldorf, Germany), and the results showed that 22 cases were the bare minimum that needed for each group to reveal a statistically significant difference between the two means. To compensate for any dropouts, 25 patients were recruited to each group.

Results

Fifty-nine patients were eligible to participate in this study. Four patients were initially excluded due to having previous cardiac surgery (two patients), suffering from renal dysfunction (one patient), declining to participate (one patient). The total number of participants who fulfilled the inclusion criteria were 55 patients. Following randomization, three patients in group-A and one patient in group-B were eliminated due to various reasons indicated in Fig. 1. The final analysis utilized data from 51 participants.

The patients' demographics and operative data (surgery type, duration of surgery, CPB time, aortic cross-clamping period) were comparable between the two groups (Table 1).

Figure 1



CONSORT flow chart of the studied cases.

The vital signs (MAP, HR), recorded intraoperatively at skin incision and at sternal retraction time-points, demonstrated significant lower values in group-A than group-B. However, vital signs before skin incision (baseline) and at sternal closure, showed statistically insignificant differences between both groups (Table 2).

The postoperative pain severity measured by visual analogue score (VAS) showed insignificant values between both groups at all time-points; eye-opening, 6 h, 12 h, 18 h, 24 h at rest and with cough after surgery, except for the VAS score at the 12th hour during cough which demonstrated significant lower value in group-B (4, IQR; 3-4.5) than group-A (4.5, IQR; 3.75–5) with P=0.01 (Fig. 2).

Regarding opioid consumption, the intraoperative fentanyl utilization was higher in group-B than group-A; (982±129.81) vs (893.85±113.39) respectively, ($P = 0.01$). The postoperative narcotic requirements, including the total amount of PCA morphine and the time of first tramadol request and its frequency of use were comparable between both groups. Further postoperative outcomes, such as time till extubation, duration of ICU and hospital stays, and overall patient satisfaction (the median score was 4 as satisfied) were also comparable between group-A and group-B (Table 3).

Discussion

In cardiac surgery patients, a planned approach to reduce postoperative pain is essential to minimize the incidence of pulmonary, cardiovascular, and endocrinal implications. Moreover, proper control of pain facilitates early tracheal extubation, rapid ambulation and prompt hospital release [10]. The common sources of postoperative pain in cardiac surgery are sternotomy, rib retraction, conduit harvest site, and drain tube site. Pain sensation, originating from the anterior chest wall, is transmitted through the intercostal nerves (T2-T6), which supply the ribs, sternum, and cutaneous tissues. Therefore, using LA agents to block peripheral nerves has been provoked in cardiac surgical settings to abolish pain transmission [2]. Pre-emptive application of LA acts as anti-nociceptive that prevents early release of the inflammatory mediators

Table 1 Demographic and operative criteria of the studied groups

	Group A (n = 26)	Group B (n = 25)	P value
Age (yrs.)	51.65 (13.04)	49.52 (13.85)	0.57
Gender			
Male	15 (57.6%)	16 (64%)	0.68
Female	11 (42.3%)	9 (36%)	
BMI (kg/m2)	23.11 (3.36)	22.68 (3.07)	0.57
History of DM (n%)	8 (31%)	6 (24%)	0.47
EF (%)	52.57 (6.04)	51.04 (6.09)	0.37
Type of surgery (n%)			
CABG	21 (81%)	19 (76%)	0.93
Valve replacement	5 (9%)	6 (24%)	
Duration of surgery (hr.)	5.48 (1.04)	5.88 (1.11)	0.19
Duration of CPB time (min)	113.77 (24.62)	108.08 (25.75)	0.42
Aortic cross clamp time (min)	88.07 (14.03)	86.88 (13.16)	0.76

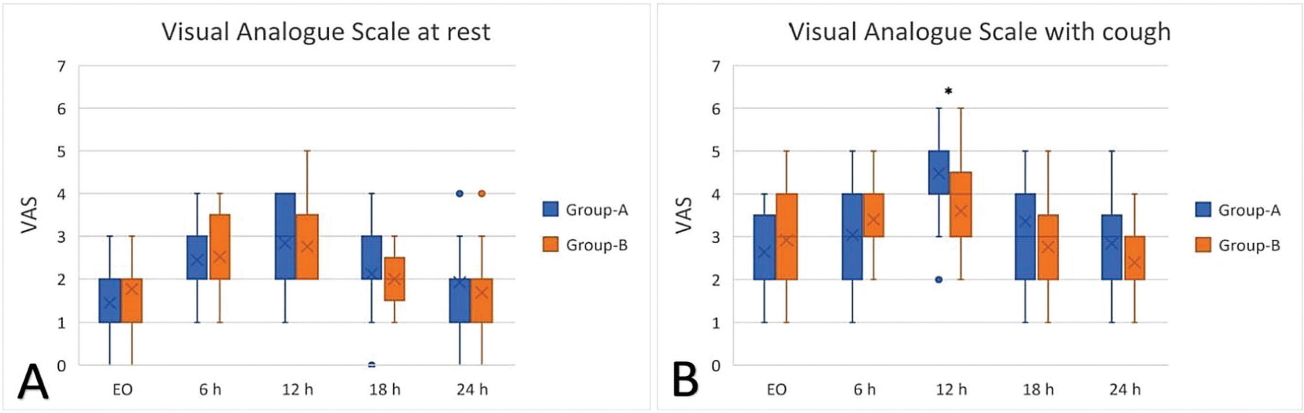
Data presented as mean (SD) and number (%). * Statistically significant at $P \leq 0.05$. BMI, body mass index; CPB, cardio-pulmonary bypass; DM, diabetes millets; EF, ejection fraction.

Table 2 Intraoperative hemodynamics (MAP – HR) of the studied groups

	Group A (n = 26)	Group B (n = 25)	P value
Basal MAP (mm Hg)	77.5 (10.13)	76.6 (11.62)	0.77
MAP Post skin incision	76.03 (11.97)	84.08 (14.87)	0.038*
MAP at sternal retraction	80.26 (11.37)	88.32 (13.80)	0.027*
MAP at sternal closure	80.73 (9.32)	80.56 (10.80)	0.95
Basal HR (beat/min)	82.23 (11.14)	83.08 (11.48)	0.78
HR post skin incision	80.61 (10.98)	87.24 (10.98)	0.036*
HR at sternal retraction	88.07 (10.22)	94.28 (10.03)	0.033*
HR at sternal closure	82.15 (10.44)	79.64 (9.45)	0.37

Data presented as mean (SD) and number (%). * Statistically significant at $P \leq 0.05$. HR, heart rate; MAP, mean arterial pressure.

Figure 2



Visual Analogue Score (VAS) for pain at rest (A) and with cough (B) at various time points over the first 24 h after surgery. Values are presented as median (IQR). EO; eye opening.

Table 3 Intraoperative and postoperative outcomes of the studied groups

	Group A (n = 26)	Group B (n = 25)	P value
Intraoperative fentanyl need (ug)	893.85 (113.39)	982 (129.81)	0.01*
Total postoperative morphine consumption (mg)	28.54 (17.17)	27.92 (15.52)	0.89
1st tramadol request (h)	10.91 (2.95)	9.75 (2.49)	0.87
Tramadol rescue doses (n%)	11 (42%)	8 (32%)	0.45
Time to extubation (h)	6.12 (2.44)	6.96 (2.23)	0.20
Length of ICU stay (h)	52.38 (5.09)	53.8 (5.97)	0.34
Length of hospital stay (day)	5.42 (1.10)	6.08 (1.80)	0.12
Patient satisfaction	4 [4-4.25]	4 [3-4]	0.12
Block related complications	0 (0.0%)	0 (0.0%)	0.99

Data presented as mean (SD), median (IQR), and number (%). * Statistically significant at $P \leq 0.05$. ICU, intensive care unit.

from the injured tissues, which are responsible for central and peripheral nervous systems sensitization [8].

In the present study, results revealed comparable pain profile over 24 h after surgery between the pre-incisional and post-incisional PSIB groups. No statistically significant differences were noted regarding; postoperative VAS scores (measured at eye-opening then every 6 h for 24 h), postoperative PCA morphine utilization, and tramadol rescue doses requirements. Also, the postoperative outcomes, including time to extubation, ICU stay, and hospitalization duration were comparable between groups. However, measurements during the intraoperative period demonstrated significantly lower fentanyl requirements and lower HR and MAP values at two stress-points (skin incision and sternal retraction) in the pre-incisional group. Otherwise, no block-related complications were detected in the two groups and the participants were similarly satisfied regarding their pain experience.

To the best of our knowledge, only one study conducted by Padala *et al.*, compared the impact of pre-incisional versus postincisional PSIB techniques on the quality of pain control in 84 patients underwent cardiac surgery involving sternotomy [9]. In agreement to our results, they stated that both techniques provided comparable VAS scores during the postoperative period. Also, the intra-operative fentanyl needed before CPB was significantly higher in postincisional group than the pre-incisional group (0.68±0.72 ug/kg vs 0.16±0.43 ug/kg; respectively, $P < 0.001$), but the total amount of opioids consumed during the first postoperative 24 h was unaffected by the timing of the block performance [11]. Although, the two groups in Padala *et al.* study showed significant differences in CPB duration and total surgery time, these confounding factors were absent in our trial, which approve the intraoperative advantage associated with preincisional block.

Few clinical trials investigated the utility of pre-emptive PSIB versus controls in different surgical sittings. Vilvanathan *et al.* enrolled two groups of 45 patients in each, underwent coronary artery bypass grafting (CABG) surgery, they performed ultrasound-guided PSIB using levobupivacaine

before skin incision to one group and the other received IV morphine as the standard analgesic regimen. Results demonstrated a significant reduction in intraoperative fentanyl and postoperative rescue opioid needs with lower pain scores at rest and during pulmonary exercise over the first 12 h in PSIB group [12]. Another trial by Chen *et al.* compared the control group to the ultrasound-guided PSIB preincisional in mediastinal mass resection through median sternotomy. The PSIB group demonstrated lower pain scores and needed 20% less PCA-sufentanil than the controls (54.05 ±11.14 μg vs. 67.67±8.92 μg; respectively, $P < 0.001$) over the course of 24 postoperative hours [13]. at last, Zhang *et al.* study reported a significant reduction in the need of sufentanil and parecoxib during open heart surgeries, along with decreased pain levels 24 h postsurgery when PSIB was given pre-emptively. Also, the extubation time [14].

Regarding the intraoperative hemodynamic stability in the pre-incisional group, our results are in consistent with Bloc *et al.* randomized-controlled trial, which recruited 35 patients to evaluate the effectiveness of preincisional ultrasound-guided PSIB versus placebo group in CABG operation. The authors noted that the preoperative PISB group required significantly lower median maximum effect-site concentrations of remifentanil and propofol to keep blood pressure and heart rate within the acceptable ranges during sternotomy [15].

Many clinical researches have reported the effectiveness of post-incisional PSIB to manage pain in cardiac surgeries. Beginning with, McDonald *et al.* study that reported PSIB for the first time in 2005. It presented a postoperative parasternal block delivered by the surgeon using and compared its effectiveness against a placebo group. Even though the study only included 17 patients, it showed a substantial advantage for the PSIB group in terms of lower postoperative pain, less opioid use, and fewer rescue doses [6]. Till, Turkmen and Mutlu who compared the postoperative PSIB with PECS-II block in open heart surgery with sternotomy and stated that PSIB supplied longer block duration with lower postoperative pain scores and less cumulative morphine consumption than the PECS II block. [16] Also, several clinical trials reported similar observations regarding the role of post-incisional PSIB to improve pain outcomes [17–20].

Although the preincisional injection of LA was applied nearly five hours before the postincisional block, a comparable analgesic impact up to 24 postoperative hours was observed, which could be related to the pre-emptive effect of the early LA administration. The concept of pre-emptive effect is further supported by the intraoperative stabilization of hemodynamics. the traditional viewpoint in previous literature believed that the timing of analgesia administration was crucial to achieve an effective decrease of postinjury pain. However, it is a restrictive and limited point of view since we now understand that pain sensitization is produced by means other than peripheral nociceptive stimulation caused by surgical incision. Noxious stimuli can trigger both peripheral and central sensitization, which intensify the pain sensation and increase analgesics requirement [21]. A systematic review and meta-analysis conducted by Møiniche *et al.* on 80 randomized clinical trial comparing pre-injury versus post-injury analgesic administration in different surgical sittings, reported that both timing of administration was equally effective in prolonging the analgesic effect and reducing opioid demand during the postoperative period [22].

There were few limitations to this study, the most significant one being that the pre-incisional block was carried out by the anesthesiologist guided by ultrasound, while the post-incisional block was carried out directly by the surgeon. In addition, there was no control group to evaluate the nerve block efficiency. However, the studies included a control group using placebo confirmed the efficiency of PSIB in reducing consumption of opioids and lowering scores of pains. So, it was not necessary to set a control group using saline infiltration to deny its pain-relieving effect. Finally, the relatively short observation duration (24 postoperative hours) that was determined to follow up pain scores and opioid requirements. However, during the first 24 h after surgery physical distress and hemodynamic swings are particularly concerning. Further research studies on preemptive PSIB with longer followâ up period should be done, so that its efficacy on chronic post-sternotomy pain can be detected in patients underwent cardiac surgeries.

Conclusions

Pre-incisional and post-incisional parasternal intercostal blocks provided comparable pain-relieving effect during the early postoperative period following cardiac surgeries involving sternotomy. However, preincisional block revealed more intraoperative benefits in terms of more hemodynamic stability and less fentanyl consumption.

Acknowledgements

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Zubrzycki M, Liebold A, Skrabal C, Reinelt H, Ziegler M, Perdas E, *et al.* Assessment and pathophysiology of pain in cardiac surgery. J Pain Res 2018; 11:1599–611.

2 Bignami E, Castella A, Pota V, Saglietti F, Scognamiglio A, Trumello C, *et al.* Perioperative pain management in cardiac surgery: a systematic review. Minerva Anestesiol 2018; 84:488–503.

3 Engelman DT, Ben Ali W, Williams JB, Perrault LP, Reddy VS, Arora RC, *et al.* Guidelines for Perioperative Care in Cardiac Surgery: Enhanced Recovery After Surgery Society Recommendations. JAMA Surg 2019; 154:755–66.

4 Brandi A.B., Stephen A.E., Mark S-S3 Pain management strategies for thoracotomy and thoracic pain syndromes. Semin Cardiothorac Vasc Anesth 2014; 18:45–56.

5 Sepolvere G, Coppolino F, Tedesco M, Cristiano L. Ultrasound-guided parasternal blocks: techniques, clinical indications and future prospects: a narrative review. Minerva Anestesiol 2021; 87:1338–1346.

6 McDonald SB, Jacobsohn E, Kopacz DJ, Desphande S, Helman JD, Salinas F, *et al.* Parasternal block and local anesthetic infiltration with levobupivacaine after cardiac surgery with desflurane: the effect on postoperative pain, pulmonary function, and tracheal extubation times. Anesth Analg 2005; 100:25–32.

7 Thomas KP, Sainudeen S, Jose S, Nadhari MY, Macaire PB. Ultrasound-guided parasternal block allows optimal pain relief and ventilation improvement after a sternal fracture. Pain Ther 2016; 5:115–22.

8 Dahl JB, Møiniche S. Pre-emptive analgesia. Br Med Bull 2005; 71:13–27.

9 Møiniche S, Kehlet H, Dahl JB. A Qualitative and Quantitative Systematic Review of Preemptive Analgesia for Postoperative Pain Relief: The Role of Timing of Analgesia. Anesthesiology 2002; 96:725–741.

10 Liu SS, Wu CL. Effect of postoperative analgesia on major post-operative complications: a systematic update of the evidence. Anesth Analg 2007; 104:689–702.

11 Padala SR, Badhe AS, Parida S, Jha AK. Comparison of preincisional and postincisional parasternal intercostal block on postoperative pain in cardiac surgery. J Card Surg 2020; 35:1525–30.

12 Vilvanathan S, Saravanababu MS, Sreedhar R, Gadhinglajkar SV, Dash PK, Sukesan S. Ultrasound-guided modified parasternal intercostal nerve block: role of preemptive analgesic adjunct for mitigating poststernotomy pain. Anesth Essays Res 2020; 14:300–4.

13 Chen H, Song W, Wang W, Peng Y, Zhai C, Yao L, *et al.* Ultrasound-guided parasternal intercostal nerve block for postoperative analgesia in mediastinal mass resection by median sternotomy: a randomized, double-blind, placebo-controlled trial. BMC Anesthesiol 2021; 21:1–9.

14 Zhang Y, Gong H, Zhan B, Chen S. Effects of bilateral Pecto-intercostal Fascial Block for perioperative pain management in patients undergoing open cardiac surgery: a prospective randomized study. BMC Anesthesiol 2021; 21:175.

15 Bloc S, Perot BP, Gibert H, Koune JD, Burg Y, Leclerc D, *et al.* Efficacy of parasternal block to decrease intraoperative opioid use in coronary artery bypass surgery via sternotomy: a randomized controlled trial. Reg Anesth Pain Med 2021; 46:671–8.

16 Turkmen S, Mutlu M. Evaluation of the effect of different block techniques on open-heart surgery in the postoperative period: a prospective observational study. Cardiovasc J Afr 2022; 33:153–6.

17 Barr AM, Tutungi E, Almeida AA. Parasternal intercostal block with ropivacaine for pain management after cardiac surgery: a double-blind, randomized, controlled trial. J Cardiothorac Vasc Anesth 2007; 21:547–53.

18 Tokgöz O, Beyaz SG, Tanrıverdi B. Effects of parasternal block and local anaesthetic infiltration by levobupivacaine on postoperative pain and pulmonary functions after offpump coronary artery bypass graft surgery. Turk Gogus Kalp Dama 2011; 19:24–9.

19 Saeidi M, Aghadavoudi O, Sadeghi MM, Mansouri M. The efficacy of preventive parasternal single injection of bupivacaine on intubation time, blood gas parameters, narcotic requirement, and pain relief after open heart surgery: A randomized clinical trial study. J Res Med Sci 2011; 16:477–483.

20 Ozturk NK, Baki ED, Kavakli AS, Sahin AS, Ayoglu RU, Karaveli A, *et al.* 'Comparison of Transcutaneous Electrical Nerve Stimulation and Parasternal Block for Postoperative Pain Management after Cardiac Surgery',. Pain Res Manage 2016; 2016:4261949.

21 Katz J, Clarke H, Seltzer ZE. Preventive analgesia: quo vadimus?. Anesth Analg 2011; 113:1242–53.

22 Møiniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. J Am Soc Anesthesiol 2002; 96:725–41.