

Local and Regional Anesthesia versus Conventional Analgesia for Preventing (PPP) in Adults and Children

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Received: 16 August 2021

Accepted: 23 February 2022

Abstract

Anesthesia is a technique for reducing or eliminating pain, in medical and dental practice, local anesthetics have a long history of efficacy and safety. Persistent postoperative pain (PPP) is caused by tissue damage so local anesthetics used to block bundles or roots of nerves in the central nervous system is one technique to prevent persistent postoperative pain (PPP). **Aim of this study** aimed to synthesize outcome data across systematic review and meta-analysis for comparing local and regional anesthesia versus conventional analgesia to prevent persistent postoperative pain in adults and children undergoing surgery. **Methods:** Online databases Medline, Pub Med, and Google Scholar of Randomized controlled trials published between 2014 and 2021. The PRISMA checklist was utilized to guide this review.. **Results:** 8 RCTs studies in the review; (2) RCTs favored epidural anesthesia for thoracotomy suggesting the odds of having PPP three to 18 months following an epidural for thoracotomy, (1) RCTs favored regional anesthesia after caesarean section, (5) RCTs also favored the infusion of intravenous local anesthetics for the prevention of PPP three to six months after breast cancer surgery. The regional anesthesia may moderate reduce the risk of developing PPP after thoracotomy and caesarean section. There is low evidence that regional anesthesia may reduce the risk of developing PPP after breast cancer surgery. **Conclusions:** This meta-analysis found that localized anesthesia has potential benefits, such as reduced post-anesthesia care unit utilization, nausea, and postoperative pain

Keywords: regional anesthesia, local anesthesia, and persistent postoperative pain (PPP).

Introduction:

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Background:

. **Conventional analgesia:** (Opioids and non-steroidal anti-inflammatory drugs)

Many patients reported moderate to severe pain after surgery, according to clinical surveys. Postoperative pain that is not well managed has negative physiological implications.. PCA has been reported to produce superior analgesia and provide patients a sense of control over their pain management than standard IM opioids. PCA is safe that it has been linked to adverse effects such as nausea, vomiting, dizziness, and respiratory depression, (1).

. Regional Anesthesia Techniques:

Regional Anesthesia (RA) aimed to build and cultivate expertise in motor skills that are in line with providing high-quality, safe patient care. Knowledge and ongoing assessment of taught knowledge and skills are all required in RA training and practice. Perioperative use of RA and analgesia may improve patient outcomes by reducing unfavourable perioperative pathophysiology. Local anaesthetics reduce permeability in peripheral neurons and inhibit action potential propagation, resulting in local anaesthesia, (1).

Local anesthetics:

In neuronal membranes, local anaesthetics bind to and inhibit voltage-gated sodium channels. The potency, length of action, onset, and resolution of impact of local anaesthetics are all different and classified into three groups: Chloroprocaine and procaine, for example, have a short duration of action and limited efficacy, Lidocaine has a moderate duration of action and a moderate potency, and Bupivacaine has a lengthy duration of action and a high potency. Some additives (epinephrine) used with local anaesthetics have the ability to change the action of onset, adequacy, and anaesthesia duration, (2).

Neuraxial Anesthesia:

Regional anaesthesia refers to neuraxial anaesthesia, which includes spinal, epidural, and caudal anaesthesia. Local anaesthetic solutions are injected into the lumbar subarachnoid region to generate spinal anaesthesia. Local anaesthetic solutions are injected into the epidural area, usually at the lumbar and thoracic levels, to produce epidural anaesthesia, (3).

. Persistent postoperative pain (PPP):

The persistent postoperative pain (PPP) was defined as a clinical discomfort that lasts more than two months after surgery without

other causes of pain, such as chronic infection or pain from a chronic illness that preceded the surgery (4). According to the International Classification of Diseases, PPP is a continuum of acute postoperative pain that may occur after an asymptomatic time and has greater intensity or different pain features than preoperative pain (5).

. Pathophysiology of Persistent postoperative pain (PPP):

It is obvious that the severity of pain caused by tissue injury is dependent on two factors; The first is proportional to the magnitude of

nociceptive signals caused by incision (6). The second is aided by peripheral and central sensitization mechanisms that increase the post-incisional pain experience for a given nociceptive input intensity. Processes involving epigenetic alterations can keep pain sensitivity going for a long time, resulting in a long-term state of pain vulnerability. Endogenous adaption, which is based on enhanced endogenous opioid activity, may help to reduce the incidence of chronic postoperative pain that may result in persistent postoperative pain.

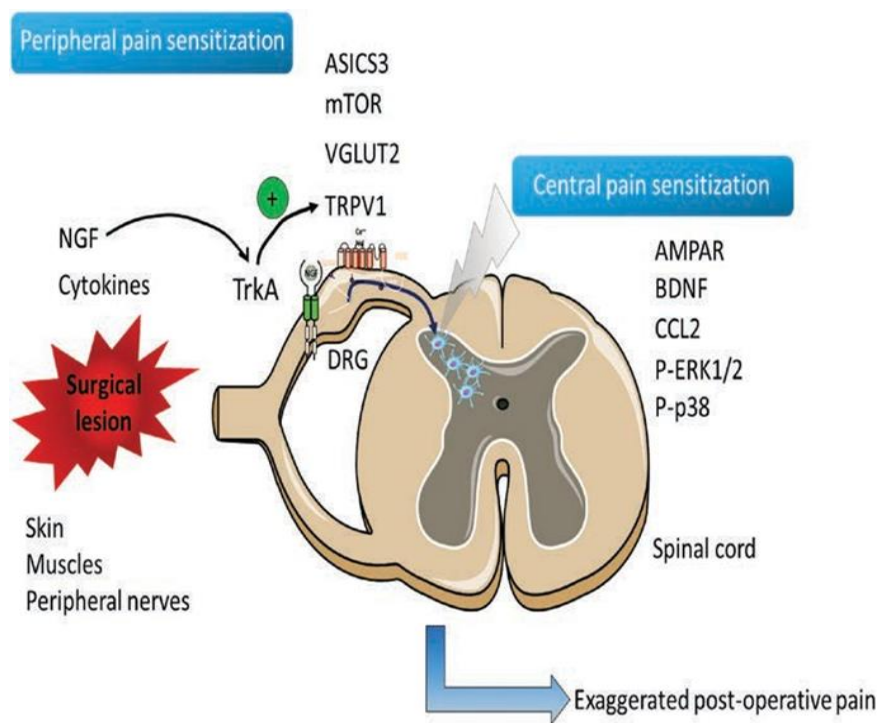


Figure (1): Mechanisms of pain sensitization after surgery leading to persistent postsurgical pain

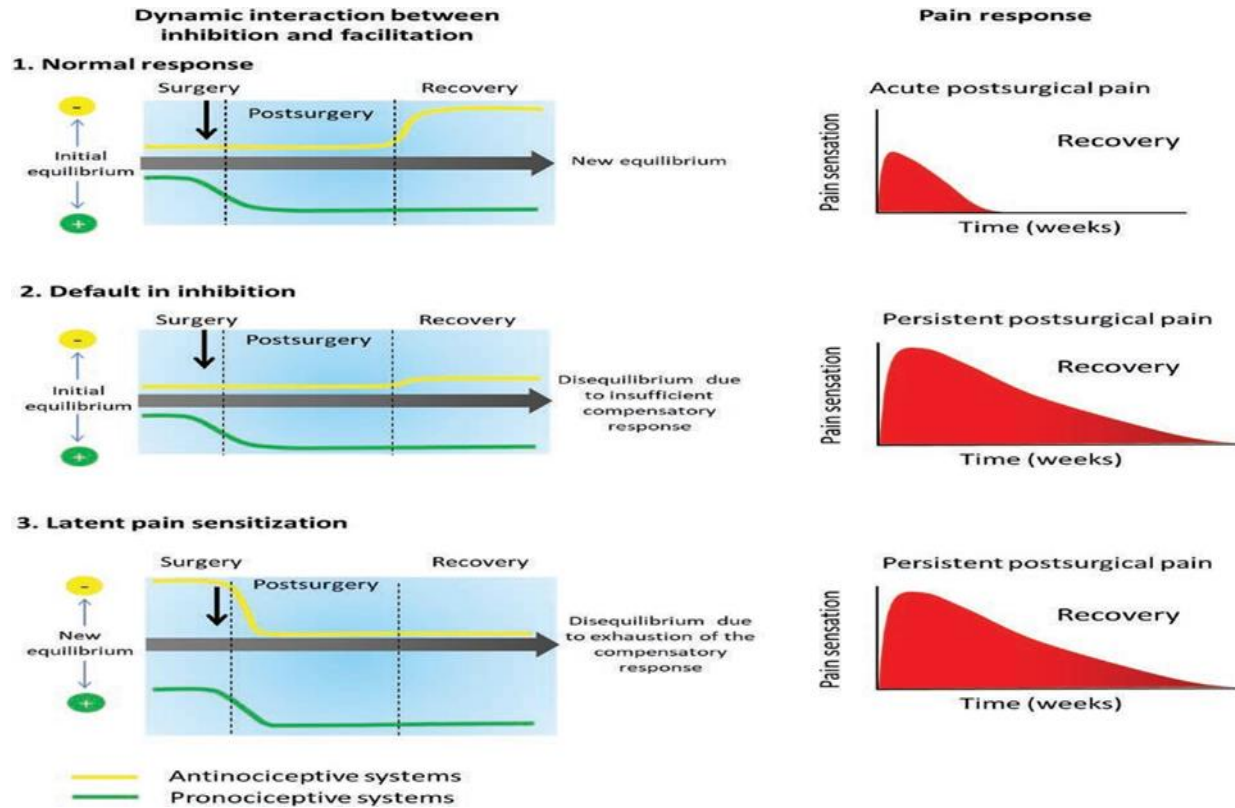


Figure (2): Persistent postsurgical pain via the engagement of pronociceptive and antinociceptive systems

Objectives:

This study was designed to compare local anaesthetics and regional anaesthesia versus conventional analgesia for the prevention of the persistent postoperative pain (PPP) in adults and children. Mention the advantage and disadvantages of local anesthesia and regional anesthesia and how overcome the disadvantages. Finally; clarify how regional anesthesia be benefit in PPP in compared with conventional analgesia.

. Study inclusion criteria

. **Participants:** Trials investigating adults and/or children undergoing elective surgery were included, regardless of the surgical approach such as laparoscopic and excluding trauma, orthopedic and emergency surgery and excluding studies focused on the effect of timing.

. **Interventions:** Studies comparing a local or regional anesthesia intervention against a conventional analgesia approach were included, regardless of the route of delivery

of the local anesthetic, the timing of the nociceptive blockade.

. **Outcomes:** We included studies assessing persistent pain beyond three months after surgery as reported in the primary studies or by a continuous pain instrument.

. **Study Design:** Only RCTs were included

Material and methods:

Search and selection:

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) standards were used to perform this systematic review and meta-analysis (7). This analysis was performed using MEDLINE, EMBASE, PubMed and Cochrane to identify Only RCTs published between 2014 and 2021 that compared local anesthetics (by any route) or regional anesthesia to any conventional (opioids or non-opioids) analgesia in adults or children were considered. Any discomfort results after three months has to be reported. Manuscripts published in any language, regardless of publishing status, were included. From 2014 to 2021, we searched the reference lists of included studies and conference abstracts by hand search.

. Study inclusion criteria:

Trials involving adults and/or children

undergoing elective surgery, regardless of surgical method, were considered, but trauma, orthopedic, and emergency surgery were excluded.

. Interventions:

Regardless of the route of distribution of the local anesthetic, the time of nociceptive blocking, or the co-administration of adjuvants, studies evaluating a local or regional anesthesia intervention to a typical analgesic technique were considered. We didn't include research that compared one local/regional approach to another, and we didn't include studies that looked at the influence of timing.

Keywords: regional anesthesia, local anesthesia, and persistent postoperative pain (PPP).

Outcomes:

We considered studies that used a continuous pain instrument to assess persistent pain beyond three months following surgery.

. Primary outcomes

Our primary outcome was persistent postoperative pain (PPP) at three or more months after surgery. We defined PPP as new pain, that not exist before the operation, but lasting beyond three months after surgery

. Secondary outcomes

Our secondary outcomes were as follows.

1. Allodynia and hyperalgesia
2. Use of pain medication
3. Adverse effects of techniques and agents used

. Study Design:

Only randomized controlled trials (RCTs) were considered. Because the effects of regional anaesthetic are immediately discernible by patients and providers, only the outcome assessor's identity was appropriate for inclusion.

Data extraction:

Data was gathered independently by the author, who assessed methodological quality using the Cochrane Risk of Bias tool and pooled data in surgical subgroups. We looked into methodological bias and heterogeneity. Only conference abstracts were available for eight of the investigations. We found any follow-up reports and collected supplementary data for three of them, (8), (9). By having an informal discussion, we were able to address any issues about data extraction, study inclusion, and quality assessment. The remaining four studies' data extraction and quality assessment were completed with the assistance of the study authors (2; 10; 11; 12).

. Assessment of risk of bias:

Following the guidelines in the Cochrane Handbook, two authors independently evaluated the methodological quality of included studies based on randomization, allocation, observer and participant blinding, selective reporting, and funding, in addition to extracting data in duplicate. Each category and study was given a score based on the likelihood of bias (low, high), along with the authors' reasoning. For each report, at least two of the review authors independently evaluated each report meeting the inclusion criteria. We contacted study authors for missing information regarding their methods. We graded study quality in a 'Risk of bias. This comprised randomization, concealed allocation, observer blinding, and intention-to-treat analysis. We extracted information on conflicts of interest and funding.. We achieved consensus by informal discussion. We judged risk of bias to be unclear, high or low. In regional anesthesia interventions, blinding of participants and anesthesia providers can be difficult and hence this criterion received less weight in the evaluation of performance bias, but not with regard to detection bias. We listed excluded studies with detailed reasons

Statistical analysis:

We searched the PROSPERO systematic review registry for related systematic review, We presented outcomes as pooled odds ratios (OR) with 95% confidence intervals (95%CI), based on random effects models (inverse variance method). We pooled outcomes reported at different follow-up intervals. We compared our results to Bayesian and classical models. We investigated heterogeneity. We assessed the quality of evidence with GRADE. We present a diagram illustrating the process of the searches and selection and we followed the recommendations of the PRISMA statements.

Data synthesis:

For evidence synthesis of function and pain following surgery, outcome reporting remains a major difficulty. Heterogeneity between researches can be classified as statistical, methodological, or clinical, with long-term studies showing the most heterogeneity. The researches are divided into main categories based on surgical intervention (breast surgery, thoracotomy, caesarean section). To pool outcomes (pain versus no pain) with continuous outcomes or to pool studies collecting data at many but varying follow-ups without including the same patient twice, (13) as shown in table (1

Table (1): Surgeries, interventions and outcomes

Study ID	Regional anaesthesia	Intervention time	Adjuvant	Study population numbers	Outcome	Continuous	Follow up
Caesarean section							
McKeen 2014	Transversus abdominis plane block	Postincision, single shot vs placebo	None	74 women were included	None	Short Form -36	6 months
Breast cancer surgery							
Tecirli 2014	Intercostal nerve block	Postincision, single shot vs control	None	109 patients	Pain/no pain	Visual Analogue Scale	3 months
Lam 2015	Paravertebral block	Not specified	None	698 participants	Pain/no pain	None	6 months
Terkawi 2015b	IV lidocaine	Preincision, continuous intra op and post-op vs placebo	None	216 patients	Pain/no pain	Visual Analogue Scale (VAS)	6 months

Gacio 2016	Paravertebral block	Single shot, preincision vs control	Parecoxib, fentanyl, morphine, and adrenaline	80 female patients,	Pain/no pain	None	6 months
Strazisar 2014	Local infiltration	Postincision, continuous post-op vs control	None	2296 patients	Pain/no pain	None	3 months
Thoracotomy							
Comez 2015	Epidural	Preincision, continuous intra-op vs control	Dexketoprofen, morphine, and fentanyl	499 participants	Pain/no pain	Visual Analogue Scale	3 and 6 months
Liu 2015	Wound irrigation	Postincision, continuous post-op vs control	Fentanyl	98 patients	Pain/no pain	None	3 months

In this table, each surgical subgroup provides an overview of the surgeries, interventions used, timing, and results observed. For the subgroups of thoracotomy, breast cancer surgery, and caesarean delivery, we combined study data. The majority of studies looked into epidural analgesia for thoracotomy, but regional anaesthesia interventions for breast surgery were more varied, with four studies looking into paravertebral blocks and several others using local infiltration and even intravenous infusions, while the most commonly used technique for caesarean section was a transverse abdominal plain block.

Results and discussion of studies:

As shown in figure (2) provides a diagrammatic schema of our search, searches were conducted from 2014 to 2021

which lead to the identification of Records identified through database searching (n = 53) and additional records identified through other sources (n = 20) to be 73 articles. Records after duplicates removed (n = 19) the Records screened by title (n = 54) and Records excluded (n = 14). Full-text articles assessed for eligibility (n = 18) and Full-text articles excluded, as observational (n = 10) Studies included in the review (n = 8). This 8 unique studies were selected for inclusion and will be assessed upon completion and represented in (2) RCTs – thoracotomy, (5) RCTs - breast cancer surgery and (1) RCT-caesarean section. We graded study quality in a 'Risk of bias' table on the basis of a checklist of design components. This comprised randomization, concealed allocation, observer blinding, and intention-to-treat analysis

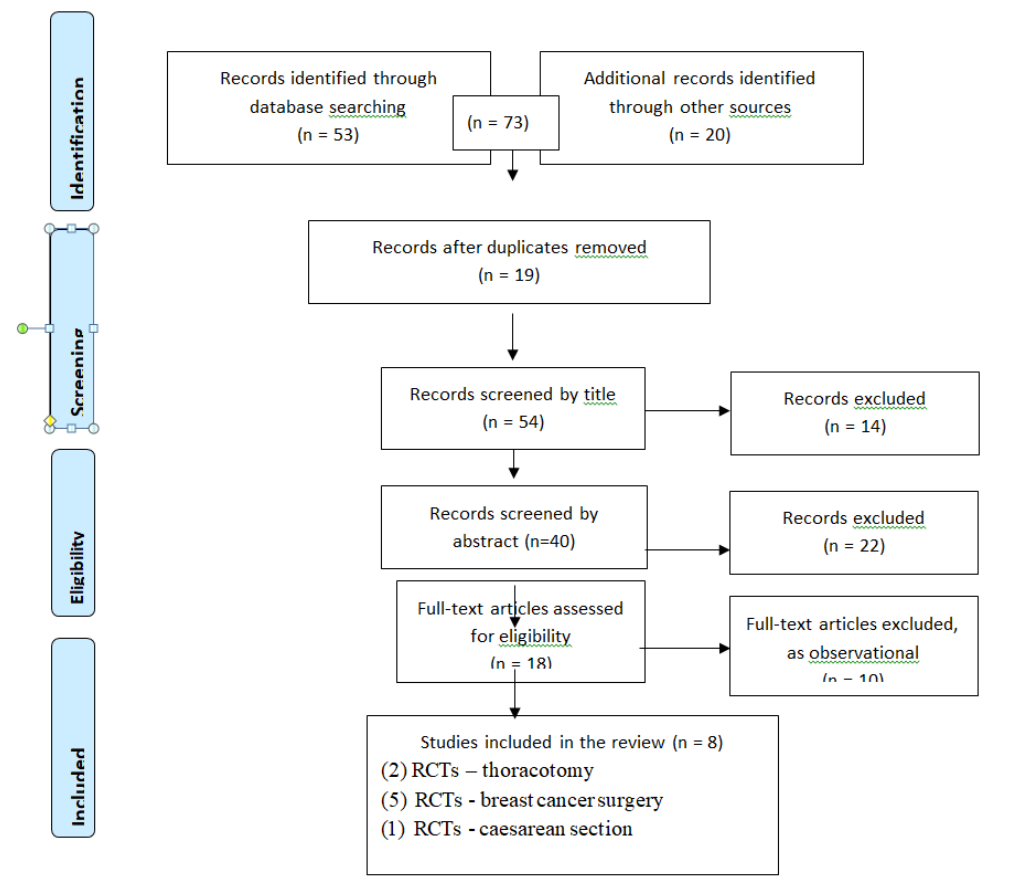


Figure (3) PRISMA flow diagram

Excluded Studies:

Other than not being relevant, studies were omitted for a variety of reasons, which are listed in the online supplement (16). 22 further studies were eliminated due to insufficient randomization, as evaluated by us. There were 18 studies in total that were not aggregated (Figure 2). The study data were not included in the meta-analysis, which was one of the grounds for not pooling them.

Outcomes:

Persistent postoperative pain (PPP) three months or more after surgery was the primary outcome. Some primary study authors identify the presence or absence of pain in their studies as pain exceeding a specific threshold on a continuous pain scale, which is similar to responder analysis. Differences in scores based on validated pain instruments, such as the visual analogue scale, were also examined (VAS). To assess the quality of the evidence, we

employed the GRADE method. Summarize the amount of the interventions under consideration, as well as the overall sum of all available data and their consistency, and balance them against the studies' internal and external validity. The study authors primarily used a dichotomous outcome, that is presence or absence of pain. They also used several continuous pain scales (verbal rating scale (VRS), visual analogue scale (VAS), numeric rating scale (NRS). two studies did not record pain as a dichotomous outcome but only used continuous pain scales (12).

Assessment of pre-existing pain and risk factors for persistent postsurgical pain:

The majority of studies did not look at pain levels at the start. Research reporting

continuous outcomes via the Short Form Health Survey (SF-36), in which some studies give baseline values for comparison, were an exception to this rule. According to (2), there is a clear benefit of regional anaesthetic for preventing persistent post-thoracotomy discomfort when limiting the analysis to (11). There are four studies (9; 14; 15; 8) that found an overall treatment impact demonstrating a definite benefit of regional anaesthesia in breast cancer surgery. Even when the trials were limited to those three that looked at paravertebral block as the intervention (9; 14), regional anesthesia was still preferred.

Table (2): Breast cancer surgery study summary of finding

local anaesthetic infusion or conventional pain control for the prevention of persistent pain after breast cancer surgery			
Case: women with breast cancer undergoing elective surgery			
Intervention local anaesthetic infusion Comparison: conventional pain control			
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect Quality of the evidence Comments (95% CI)
	Assumed risk	Corresponding risk	
	Control	Continuous intravenous local anaesthetic infusion	
Pain 3 -6 months after breast cancer surgery measured using differences in scores based on validated pain scales	109 patients - Tecirli 2014 698 participants- Lam 2015 216 patients- Terkawi 2015b 80 female patients,- Gacio 2016 2296 patients- Strazisar 2014		
Adverse effects of local anaesthetic infusion not reported			

Table (3): Caesarean section surgery study summary of finding

local or regional anaesthesia for the prevention of chronic pain after caesarean section				
Case: women after caesarean section				
Intervention: local or regional anaesthesia				
Comparison: conventional pain control				
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Quality of the evidence Comments (GRADE)
	Assumed risk	Corresponding risk		
	Control	Local or regional anaesthesia		
<p>PPP 3 to 8 months after caesarean section</p> <p>as new pain that did not exist before operation, measured by differences in scores based on validated pain scales.</p>			<p>OR 0.46 (0.28 to 0.78)</p>	<p>Event rates of persistent pain after caesarean section are reported around 10% The number of women needed to be treated for one woman to benefit from regional anaesthesia after caesarean section was 19</p>
	<p>Study population 74 women</p>			
<p>Adverse effects of local or regional anaesthesia not reported</p>	<p>Not estimable</p>			<p>Adverse effects of local or regional anaesthesia after caesarean section due to low frequency</p>

Null bias:

The incidence of 'null bias' is related to insufficiently well-delivered interventions. Insufficient pain control in the initial postoperative period is reported in a number of studies, as shown by insignificant variations in pain levels between groups preoperatively or equal need for rescue analgesic drugs in the immediate postoperative period, (10, 14).

Quality of the evidence:

The quality of the evidence has some limits. The conclusions of our review could be harmed by performance bias. Several trials solely used adjuvants in the experimental group, which could introduce bias, however this had no effect on the overall outcomes for breast cancer surgery and thoracotomy. Due to insufficient outcome data and a lack of allocation concealment, the study is vulnerable to bias.

Conclusion:

To lessen the likelihood of persistent postoperative pain (PPP) beyond three months after surgery, patients receiving open thoracotomy should choose epidural anesthesia, and women undergoing breast cancer surgery should consider paravertebral block. Using epidural anesthesia following a thoracotomy may lessen the chance of residual pain months later. The evidence for regional anesthesia in reducing persistent pain after surgery has grown to the point where eight randomized trials suggest that regional anesthesia can reduce the risk of persistent postoperative pain beyond three months after many surgical procedures. The strongest and most consistent evidence is for epidurals for thoracotomy and paravertebral blocks for breast surgery.

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To cite this article: Nahed F. Abo-Elmatey, Enas W. Mahdy, Zainb M. Abd-Elwahab. Local and Regional Anesthesia versus Conventional Analgesia for Preventing (PPP) in Adults and Children. *BMFJ* 2022;39(1):204-216. DOI: 10.21608/bmfj.2021.91063.1458