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Impact of Combining Each Adjuvant, Morphine, Buprenorphine, and Fentanyl on Anaesthesia Onset Time and Postoperative Analgesia Compared to Other Combinations for Brachial Plexus Block: A Systematic Review and Meta-Analysis

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Abstract

Blocking Brachial plexus has become increasingly preferred in upper limb and shoulder surgeries because it provides reliable surgical anaesthesia, prolonged postoperative analgesia, limb immobilization, and decreases the requirement for general anaesthesia. and its associated adverse effects. Ultrasound guidance permits for precise deployment of needles and effective deposition of local anaesthetics, rapid onset of block, improved patient satisfaction, and a lower risk of vascular injury. Opioids such as morphine, fentanyl, and buprenorphine have been explored as adjuvants to local anaesthetics to further enhance block characteristics. This meta-analysis examined the effectiveness and safety of incorporating morphine, fentanyl, or buprenorphine as adjuncts to brachial plexus anaesthesia in patients undergoing arthroscopic shoulder or other upper-limb procedures. A thorough and systematic search of the literature was carried out in databases such as PubMed, Google Scholar, Science Direct, and additional sources to identify randomized controlled trials that compared these opioid adjuvants with placebo or no supplementary agent. Outcomes assessed included onset time of sensory block, duration of postoperative analgesia, and incidence of complications. The Cochrane risk-of-bias approach was implemented for evaluating bias, and statistical investigation was executed with Review Manager 5.4 software. Thirty-five randomized controlled trials involving 2335 patients were included. Pooled analysis demonstrated a statistically significant improvement in analgesic duration with opioid adjuvants compared to control groups ($P < 0.01$; $Z = 7.37$; $I^2 = 96\%$). Buprenorphine showed a greater impact on reducing onset time. Adverse effects were comparable across groups. Relying on the GRADE structure, the quality of evidence for prolonged analgesia was high. The co-administration of morphine, fentanyl, or buprenorphine to local anaesthetics in blocks of the brachial plexus substantially enhances sensory and motor block duration and additionally provides postoperative analgesia without increasing adverse effects, offering efficacy comparable to other regularly used adjuvants.

Keywords: Brachial Plexus Block, Buprenorphine, Fentanyl, Morphine, Opioid Adjuvants, Postoperative Analgesia.

Introduction

Anaesthetizing brachial plexus numbs the whole upper limb, spanning shoulder to fingers. The technique employed to block the brachial plexus varies according to the area of operation, the patient's body type, pre-existing medical issues, expertise of the performer, presence of gadgets and any specific anatomical variants. Upper arm procedures can be blocked utilizing the axillary, infraclavicular, supraclavicular, or interscalene approaches (1-3). These blocks are particularly advantageous in both outpatient and inpatient surgical settings for a wide range of patients and procedures. Continuous catheter procedures can increase the duration of analgesia, allow for earlier mobilization, improve rehabilitation, and perhaps lead to shorter hospital stays and improved functional outcomes in major cases (4). Regional anaesthesia approaches provide multiple benefits outperforms general anaesthesia by restricting the area of anaesthesia, improving patient satisfaction,

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shortening hospital stays, and cutting total healthcare expenditures (5). One of these techniques is the brachial plexus block, which is today the standard anaesthetic strategy for most upper extremity procedures (6). Many adjuncts have been placed with local anaesthetics (LA) in order to enhance postoperative analgesia (7). However, the search for the best addition that offers superior pain relief following surgery, earlier onset of sensory and motor blockage, and lesser side effects persists. Regional methods are better than inhalational techniques, providing superior perioperative pain management. The level of discomfort experienced within the first day has a significant impact on the risk of chronic pain: Regional anaesthesia can be instrumental in reducing this risk and improving patient outcomes (8). Upper extremity surgeries are a significant source of pain that impacts patient satisfaction. This review aims to analyze primary clinical studies on the use of opioid- local anaesthetic combination on upper limb procedures. This may decrease undue postoperative opioid use and its consequences (9). Clinical studies have shown that opioids are helpful in addressing short- and medium-term pain, resulting in an opioid-centric strategy to pain management and contributing to the opioid problem. Using a combination of pharmaceuticals that function through diverse processes is often more successful than relying entirely on one mode, offers a higher degree of safety and lesser adverse effects (10). Figure 1 depicts the several nerves classified as part of the plexus.

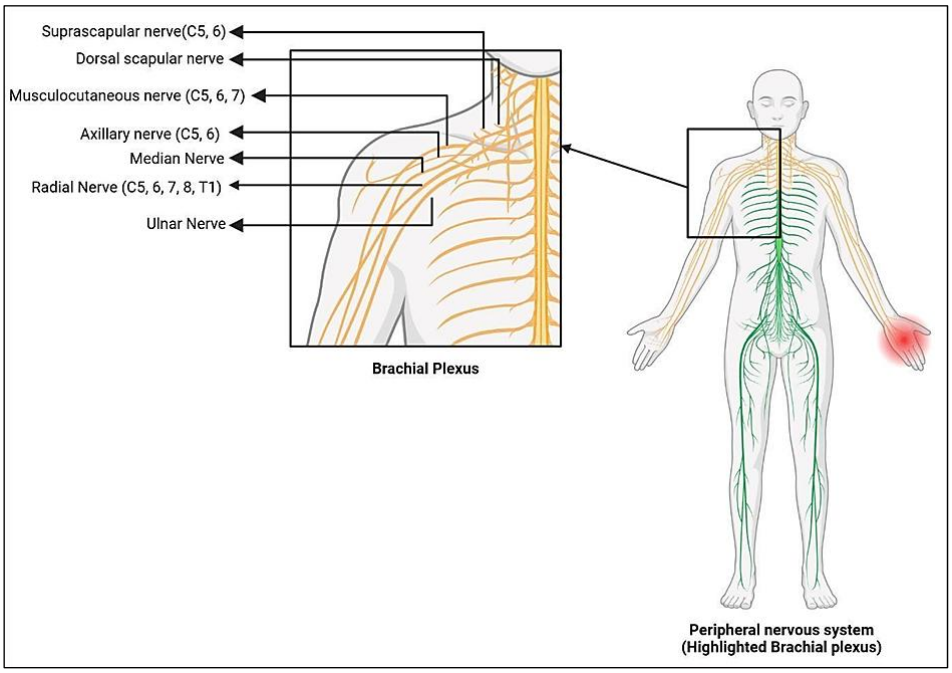

Figure 1: Representation of Brachial Plexus

In Figure 1, the diagram illustrates the brachial plexus and its associated peripheral nerves, including the suprascapular, dorsal scapular, and ulnar nerves**.** The use of adjuvants like morphine, fentanyl, and buprenorphine in brachial plexus blocks has gained prominence due to their potential to enhance anaesthetic efficacy and improve postoperative outcomes. However, there remains variability in clinical practice regarding their optimal use, dosing, and impact on key outcomes like block duration, analgesia, and complications. Current literature is fragmented, and the lack of consolidated evidence poses challenges for clinicians in making evidence-based decisions. This meta-analysis evaluates the efficacy and safety of opioid adjuvants in improving sensory block onset, postoperative analgesia duration, and overall outcomes, providing evidence for optimized clinical practices.

The significance of this study is underscored by the increasing preference for brachial plexus blocks in upper extremity surgeries due to their enhanced analgesic effects and reduced reliance on general anaesthesia. By examining opioid adjuvants, this research addresses critical gaps in pain management practices, ultimately aiming to improve postoperative outcomes and patient satisfaction.

Methodology

This review adopted the Cochrane Handbook for Systematic Reviews' methodological standards and the disclosure guidelines specified by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (11). Before beginning the literature search, the study methodology was prospectively filed in the International Prospective Register of Systematic Reviews (PROSPERO) under the ID CRD42024533277 on April 19, 2024. The review questions were generated utilizing the Population - Intervention – Comparison – Outcome - Study (PICOS) paradigm.

The specific PICOS criteria applied in this study are as follows:

a) Participants: Adult patients (≥18 years) undergoing upper extremity surgeries, including shoulder arthroscopy, under brachial plexus block;
b) Interventions: Use of morphine, fentanyl, or buprenorphine as adjuvants to local anaesthetics during brachial plexus block;
c) Comparisons: Patients receiving local anaesthetics combined with morphine, fentanyl, or buprenorphine compared to those receiving local anesthetics alone or other combinations.;
d) Outcomes: Primary objectives included the beginning time of sensory block and the time frame of postoperative analgesia. Secondary outcomes were negative outcomes and morbidity linked with the use of adjuvants.
e) Study Design: Randomized controlled trials (RCTs), prospective, retrospective, and cross-sectional analytical studies comparing adjuvants for brachial plexus block.

Search Strategy and Study Identification

The systematic electronic searching approach was devised to do an exhaustive search for relevant studies. The databases MEDLINE, Pubmed, ScienceDirect, and Google Scholar to identify published and pre-published studies reporting outcomes related to interventions for the opioids (till 19th December 2024). The filters “Time” from 2019 to 2023 (Google Scholar, PubMed and ScienceDirect) and “Article type” applied to Research articles (ScienceDirect), “Languages” to English (ScienceDirect and PubMed). The search strategy included keywords/ medical Subject Heading/Entree terms such as ‘morphine and peripheral nerve blockade and brachial plexus block and clinical trials’, ‘buprenorphine and peripheral nerve blockade and brachial plexus block and clinical trials’, ‘fentanyl and peripheral nerve blockade and brachial plexus block and clinical trials.’

The systematic electronic search strategy was meticulously designed to execute a comprehensive and exhaustive review of literature examining the efficacy of opioid interventions in conjunction with peripheral nerve blockade, particularly focusing on the brachial plexus block—a pivotal technique in regional anaesthesia. This block is renowned for its ability to provide significant analgesia, particularly in upper extremity surgeries, and optimizing opioid use in this context is crucial due to the potential for opioid-related adverse effects and the on-going opioid epidemic.

To ensure that our review encompassed a wide-ranging spectrum of insights, multiple databases were systematically queried, including MEDLINE, PubMed, ScienceDirect, and Google Scholar. This strategy sought to include both published and unpublished data on opioid medications in brachial plexus anaesthesia up to December 19, 2024.

To refine and focus our search results, specific filters were applied. The timeline selected spans from 2019 to 2023, incorporating recent advancements and clinical trials that reflect evolving practices and standards in pain management. Research articles were specifically emphasized on ScienceDirect to ensure methodological rigor and relevance, while language restrictions to English in both ScienceDirect and PubMed maintained accessibility to studies relevant to an international audience.

The search strategy employed a comprehensive array of keywords, Medical Subject Headings (MeSH), and entry terms, which included robust combinations such as 'morphine and peripheral nerve blockade and brachial plexus block and clinical trials,' ‘buprenorphine and peripheral nerve blockade and brachial plexus block and clinical trials,’ and ‘fentanyl and peripheral nerve blockade and brachial plexus block and clinical trials.’ Each keyword was selected following an extensive review of existing literature to ensure, that critical aspects of opioid pharmacology,

efficacy, and comparative outcomes were thoroughly covered.

Moreover, this search strategy is grounded in the principles of evidence-based medicine, aiming to ensure that the findings translate to improved clinical practice. By synthesizing data from various studies, we aim to elucidate the nuanced role of opioids in enhancing analgesic efficacy when used in conjunction with nerve block techniques. This analysis will potentially elucidate optimal dosing strategies, timing of administration, and any synergistic effects that may occur when combining regional anaesthetic techniques with opioids. Ultimately, this comprehensive review is poised to contribute significantly to the existing body of knowledge, offering informed recommendations that align with contemporary pain management practices while simultaneously addressing the imperative for opioid stewardship in clinical settings.

Inclusion and Exclusion Criteria

We considered data from randomized controlled trials (RCTs) of adult patients aged eighteen and beyond who experienced the blockage of the brachial plexus for the upper extremity procedures. Eligible studies had to report on the use of morphine, fentanyl, or buprenorphine as adjuvants specifically in conjunction with local anaesthetics and be full-length articles. Exclusions encompassed case reports, editorials, preclinical studies, epidemiological studies, and descriptive studies without interventions for brachial plexus blocks with these opioids, along with abstracts, unpublished reports, animal studies, and in vitro studies. Additionally, studies with sample sizes of fewer than 15 patients, paediatric populations (<18 years), significant comorbidities affecting pain management, and those utilizing local anaesthetics with opioid adjuvants outside of morphine, buprenorphine, or fentanyl were excluded. Furthermore, studies failing to report critical outcomes such as onset time or postoperative duration of the block were also omitted from this analysis.

Study Selection and Data Extraction

The review was prepared in accordance with the PRISMA 2020 reporting standards for systematic reviews and meta-analyses (11). Study eligibility was assessed through a two-stage screening protocol, beginning with an initial review of titles and abstracts, followed by a detailed examination of the full texts. Three independent reviewers evaluated the titles and abstracts using predefined inclusion criteria. Articles meeting these criteria were subsequently imported into the Rayyan Professional web-based screening platform for further assessment. Each study was categorized as "include," "maybe," or "exclude." Those designated as "include" underwent further full-text assessment by the authors Studies marked as "exclude" were removed from consideration, while those in the "maybe" category were discussed with the fourth author. The ultimate choice for studies with randomized control (RCTs) was determined through discussion and consensus among all four authors.

Two writers' extracted data from pertinent research, comprising the number of authors, publication period, entire sample size, and basic patient characteristics, using an established data collecting form. Both authors recorded the clinical characteristics of all included trials and organized them into tables.

The data were extracted: author, total sample size, number of samples in a group, study design, number of groups, targeted nerve, type of surgery, mean age, onset of sensory block, duration of analgesia and outcomes detailed in the included RCTs.

The primary endpoints evaluated in this review pertained to the modulatory impact of incorporating opioid adjuvants—namely morphine, buprenorphine, and fentanyl—into local anaesthetic regimens on both the latency of sensory blockade initiation and the temporal persistence of analgesic efficacy within the context of brachial plexus anaesthesia. For each eligible investigation, the time of starting of sensory block and the total time of analgesia were systematically abstracted and documented as mean estimates accompanied by corresponding standard deviations (SD). In instances where critical study variables were incompletely reported — such as mean demographic characteristics, sensory block latency, analgesic duration profiles, or the precise concentrations of administered adjuvants — the respective study investigators were approached on more than two separate occasions to procure supplemental or clarificatory methodological and outcome data.

Risk of Bias Assessment

Two reviewers independently appraised the methodological rigor of the included randomized controlled trials using the Cochrane Risk of Bias Assessment Tool version 2.0 (RoB 2). This appraisal encompassed the evaluation of potential systematic errors across multiple methodological domains, including random sequence generation, concealment of allocation procedures, blinding of participants and study personnel, blinding of outcome evaluators, and completeness of outcome data, selective outcome dissemination, and additional ancillary sources of bias. The risk-of-bias determinations for each trial were undertaken independently by both assessors, with any discrepancies in judgment reconciled through deliberation and consensus. The synthesized outcomes of these evaluations were subsequently collated and illustrated using structured graphical representations. Instances of unresolved disagreement were further adjudicated in consultation with the corresponding author.

Summary Measures and Synthesis of Results

Analytical meta-analysis has been conducted utilizing Review Manager Version 5.4 software. The qualitative analysis was done on the extracted data from the included studies. In general, statistically significant value <0.05 and 95% confidence interval (CI) were calculated. The heterogeneity of pooled results was assessed using the I-square (I2) test, wherein values < 40%, 40-60% and >60% were considered to represent low, moderate and high heterogeneity respectively. A random-effect model was applied to analyse the data due to significant heterogeneity and sample size. Subgroup analysis was performed for type of adjuvants and concentration of adjuvants to find the contributing factors to inconsistences across the analysed studies.

The sub-group analysis was also performed based on adjuvants type and subgroup-analysis based on concentration was done to the fentanyl due to availability of data to evaluate the cause of heterogeneity among study results. These analyses stratified studies based on key variables such as the type of adjuvant used (morphine, buprenorphine, fentanyl) and dosage variations. Subgroup analyses aimed to identify whether these factors contributed to variations in onset time and postoperative duration across studies. Heterogeneity was initially assessed using the I2 statistic and chi-squared test, and substantial heterogeneity prompted further investigation through subgroup analysis. The results of these analyses were visually represented using forest plot generated in RevMan 5.4 software to assess differences in pooled effect sizes between subgroups.

Results

The literature scan yielded 5,645 articles, of which 173 articles sought for retrieval and 85 articles underwent full text review and 42 reports were included from 39 studies in the final analysis. The PRISMA diagram depicts the study decision-making process (Figure 2). We identified 05 studies that used morphine as an adjuvant, 09 and 21 studies that used buprenorphine and fentanyl as an adjuvant, respectively. These included studies have a total of 1171 patients in onset time of sensory block and a total of 1199 patients in duration of post-operative analgesia interventions (12-35).

The 39 studies addressed in the above analysis have been generated from 06 countries, i.e., India [26], Iran [02], Ethiopia [01], Egypt [07], China [01], and Bangladesh [02]. The patients reported in these studies have undergone various types of upper-arm surgeries including hand embolectomy, shoulder arthroscopic surgery and forearm and wrist surgeries. Surgeries in 36 studies involved use of ropivacaine, bupivacaine, lignocaine, levobupivacaine and lidocaine in combination with either morphine or buprenorphine or fentanyl. The dose of fentanyl ranged from 50 to 100 µg or 0.1 to 1 µg/kg. Another study reported the use of 2 different drugs/trials; thus, each experiment was analysed separately in the meta - analysis, presented as such by researchers (36-50). The details of study groups and adjuvants concentrations are given in the Supplementary Table 1.

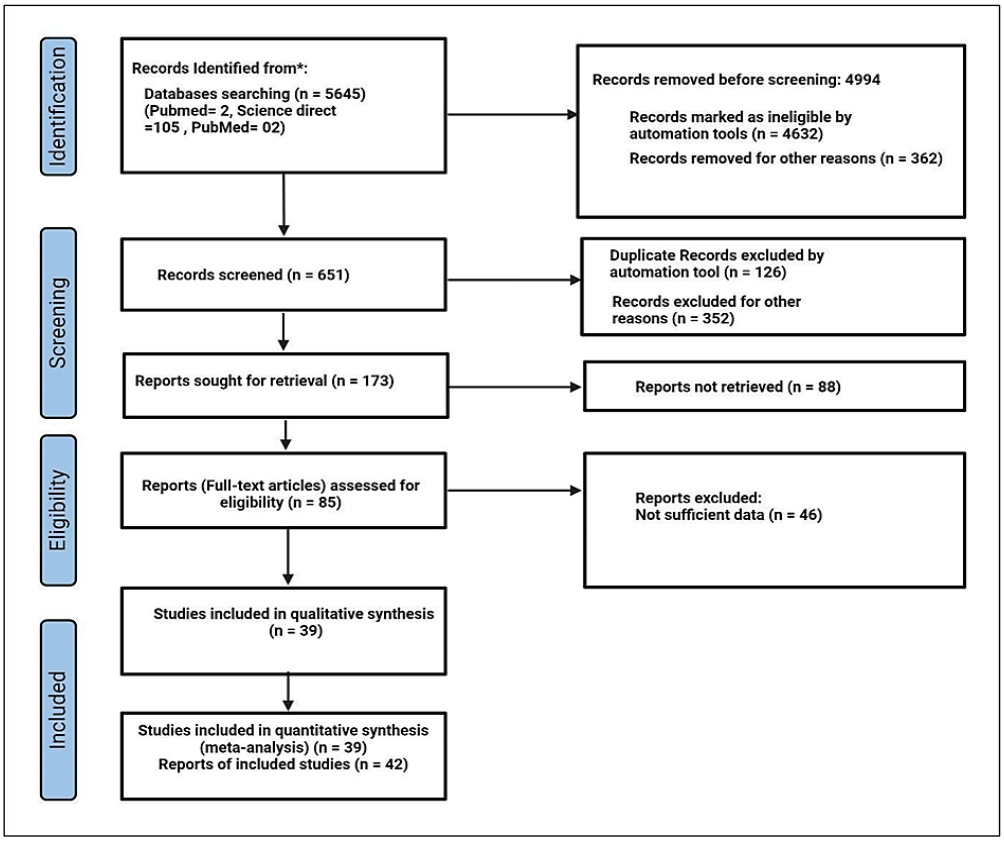

Figure 2: PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)

Risk of Bias Assessment

The threat of bias assessments was used to look at the study's quality and potential bias. This analysis included 42 randomised controlled trials. However, 21 of the above were at low risk, while 6 were at higher risk. Figure 3 and Supplementary Figure 1 present an illustration of the risk of bias. A risk of bias evaluation was conducted to examine the study's quality and potential bias. Among the 42 studies 41 trials acknowledged randomization, while 40 studies included the details of disguised allocation. However, five studies were conducted without blinding for assessment of outcomes, and six studies did not reveal the details of specific outcomes (14-16, 45) (Supplementary Figure 1).

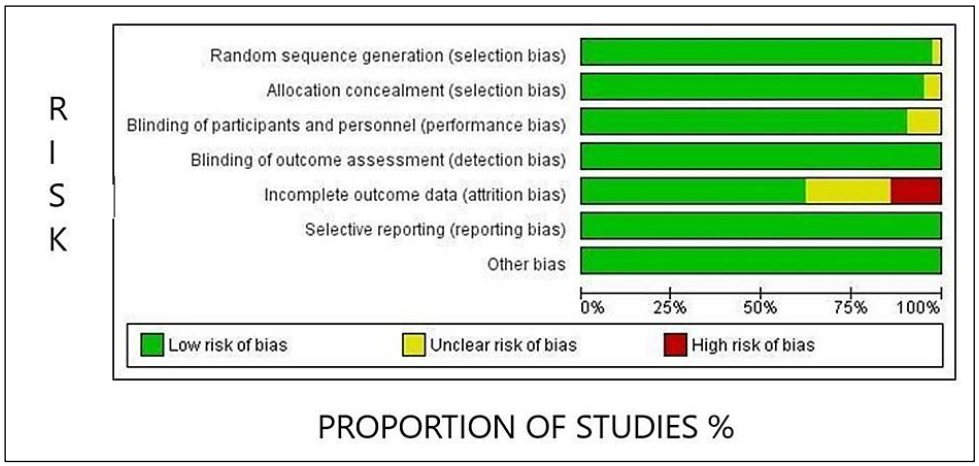

Figure 3: The General Probability of bias has been Evaluated Employing the Cochrane Collaboration Technique, with Red Indicating High Bias, Green Mild Bias, and Yellow Indicating Ambiguous Bias

Primary Outcome: Effect of Adjuvants Combination on Onset Time of Sensory Block

A total of 35 RCTs with 1171 patients in the morphine, buprenorphine and fentanyl group and 1164 patients in the control/other combination group was reported for the onset of sensory block. Pooled analysis denoted statistically significant ($P < 0.01$) (Figure 4) difference between anaesthetic with the combination of drug of interest and control group/other combinations (Z = 7.37; 95% CI: 95%; I2 = 96%; $P < 0.01$).

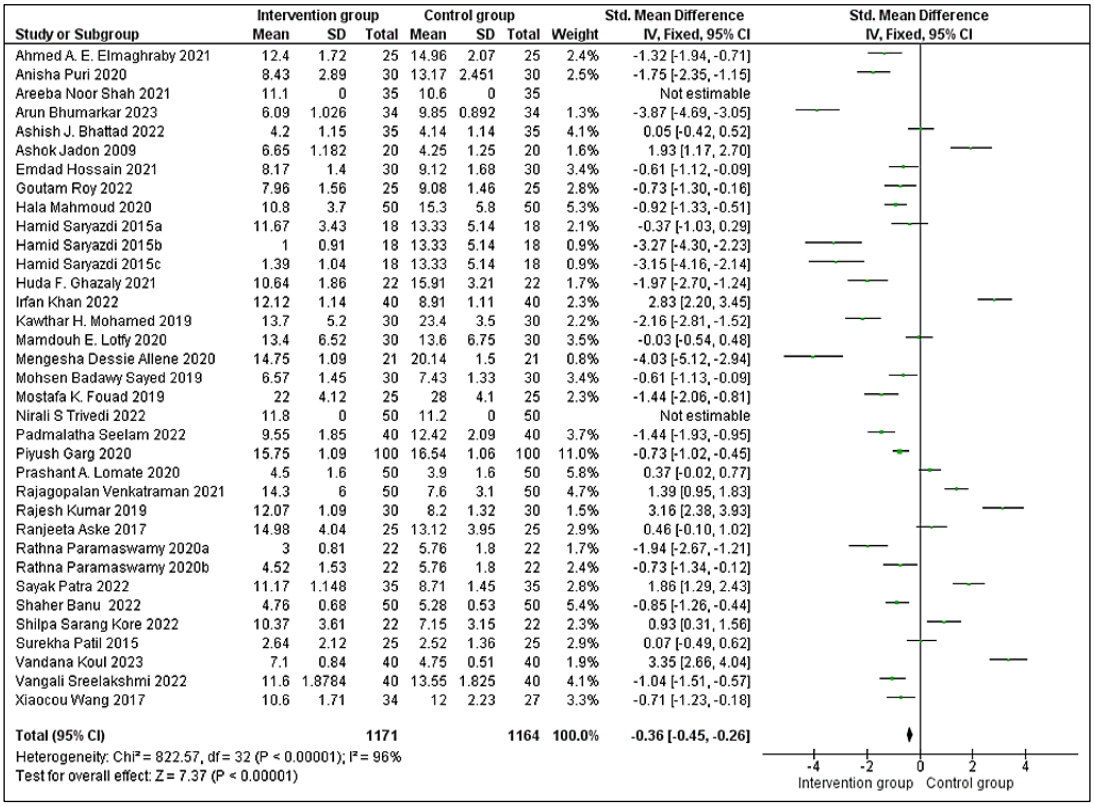

Figure 4: Forest Plot Depicts Standardized Mean Differences in Sensory Block onset between Groups, with Confidence Intervals and Notable Heterogeneity across Studies

The first sign of sensory block (onset) was defined as the length of time interval between the entire injection of the drug and the total loss of pinprick feeling. A high heterogeneity (I2 = 96%) suggests considerable variation between the studies, particularly due to differences in the types of local anaesthetics used, dosage of the adjuvants in the overall analysis. The subgroup study on the initiation of sensory block of adjuvants indicated that the three different adjuvants morphine ($P < 0.05$), fentanyl ($P < 0.01$) and buprenorphine ($P < 0.01$) in combinations with other controls exhibited significant difference on onset of sensory block. The impact of opioids on the onset of sensory block as follows, Buprenorphine > Fentanyl > Morphine. The conjoined judgment of the subgroup analyses did reveal a most notable effect, wherein the statistic Z = 7.37 did pronounce a difference of high significance betwixt the compared cohorts. This divergence did most assuredly incline in favour of the intervention assemblies, particularly with regard to the hastened advent of sensory blockade shown in Figure 5.

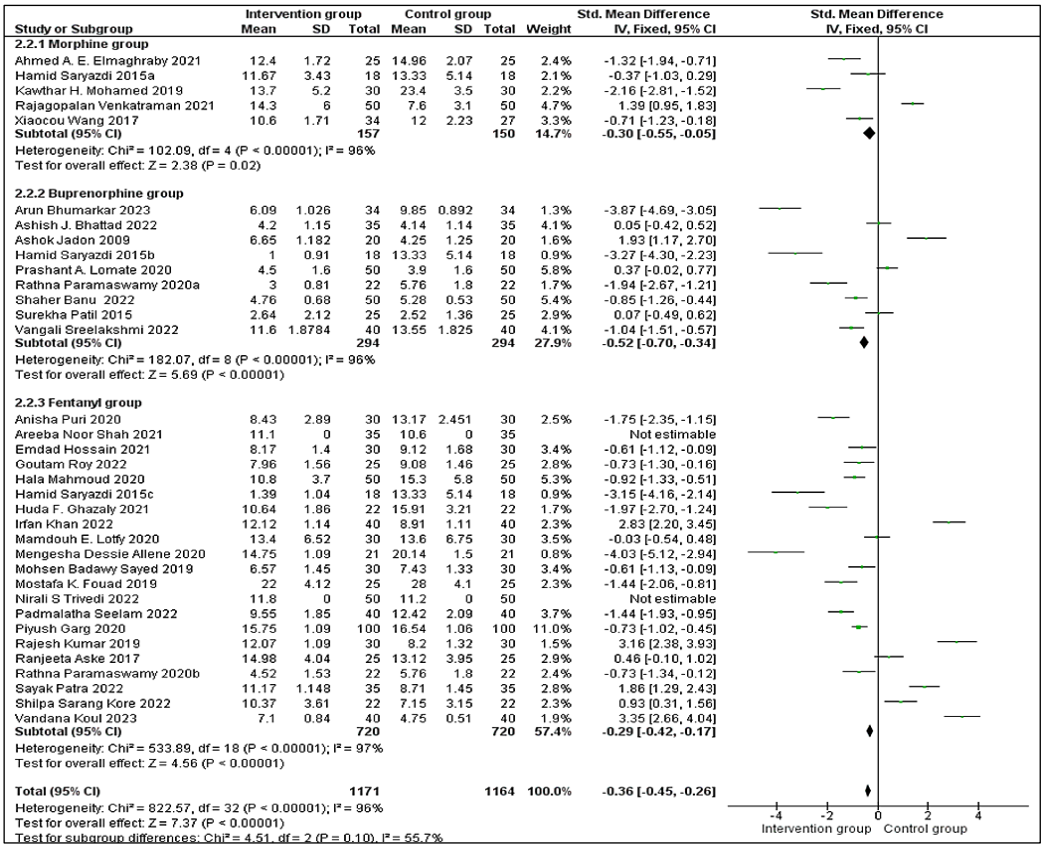

Figure 5: Forest Plot Presents Subgroup Analysis of Adjuvants Affecting Sensory Block Onset, Showing Effect Sizes, Confidence Intervals, and Statistical Significance

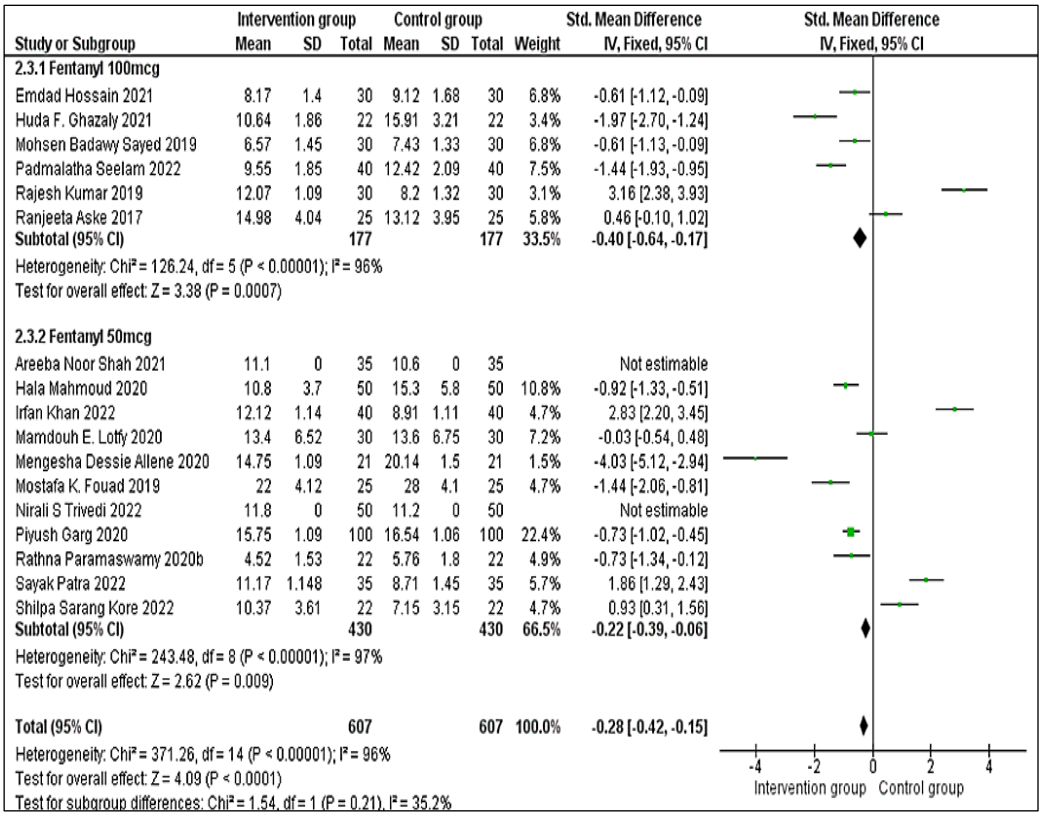

Figure 6: Forest Plot Compares Fentanyl 100 µg and 50 µg Subgroups, Showing Standardized Mean Differences, Confidence Intervals, Heterogeneity, and Overall Significant Effects

The subgroup analysis on the concentration of adjuvant (Fentanyl) showed that 100µg and 50µg of fentanyl both showed significant (P < 0.01) results in onset time. The concentration of fentanyl (100µg) was more statistically significant (*P* < 0.001) than 50µg (*P* < 0.01) in onset of sensory block shown in Figure 6.

Secondary Outcome: The influence of the compounded adjuvants upon the onset and continuance of postoperative analgesia — in its full and collective measure.

The total time of analgesia or the duration was defined as the time between the first recue medication and the infusion of first anaesthetic. A total of 1199 patients were in the morphine, buprenorphine, fentanyl combinations groups, and 1199 patients were in the other drug combinations group. Pooled analysis did not show any statistically significant (*P* = 0.90) difference between anaesthetic with the combination of drug of interest and control group/other combinations (Z = 0.12; 95% CI: 95%; I2 = 99%; *P* = 0.90) (Figure 7). This research did reveal that no notable variance was discerned among the several reckonings of the chosen drugs— morphine, fentanyl, and buprenorphine — in the length of analgesia solace afforded to the patient after the surgery was done.

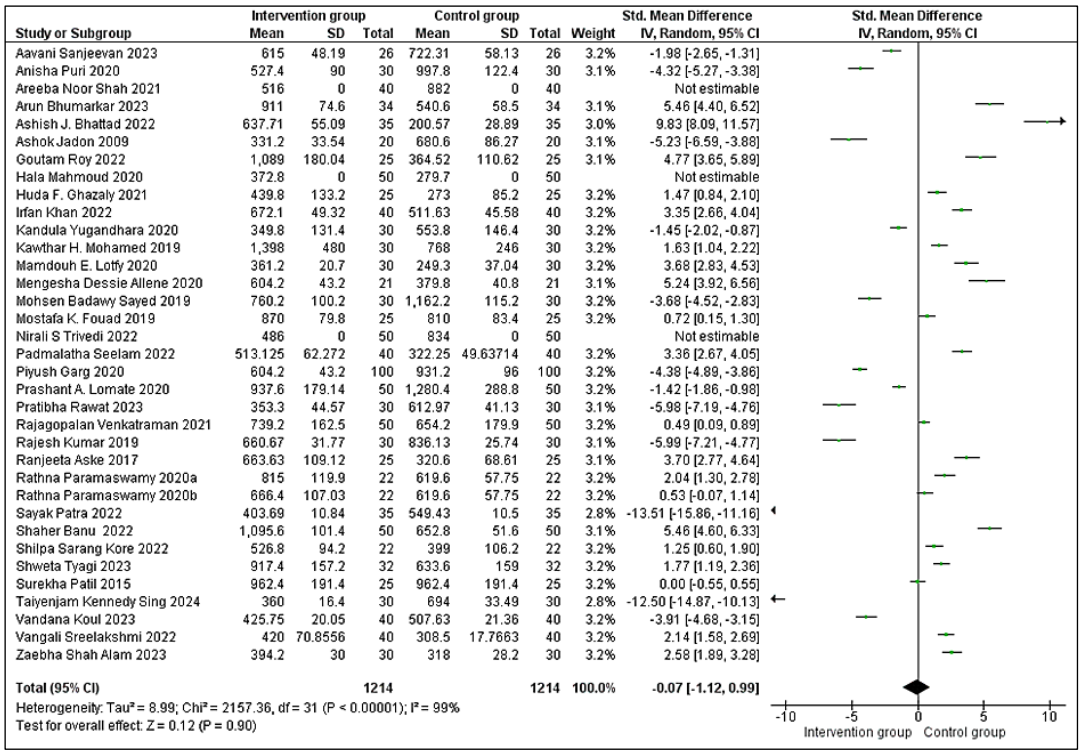

Figure 7: Forest Plot Summarizes Postoperative Analgesia Duration, Showing Standardized Mean Differences, Study Weights, Confidence Intervals, and Heterogeneity among Brachial Plexus Block Studies

The subgroup analysis indicated that the forest plot favoured the control group where bupivacaine and ropivacaine was used to treat rather than the morphine combination (*P* = 0.07). Rather than morphine it favoured Dexamethasone-ropivacaine, Dexamethasone--Bupivacaine, and rather than buprenorphine. It favoured control group/ other combinations significantly (*P* < 0.05) such as Verapamil, dexmedetomidine, tramadol, dexamethasone, diclofenac, adrenaline, normal saline, hyaluronidase, (Supplementary Table 1). Fentanyl was found to be less significant (*P* = 0.15) in postoperative time of analgesia, but results are in favour rather for buprenorphine or morphine (Figure 8). In the sub-group analysis based on the concentration of fentanyl, it was found that 100 µg showed extend duration of analgesia than the 50µg fentanyl (*P* = 0.90) (Figure 9).

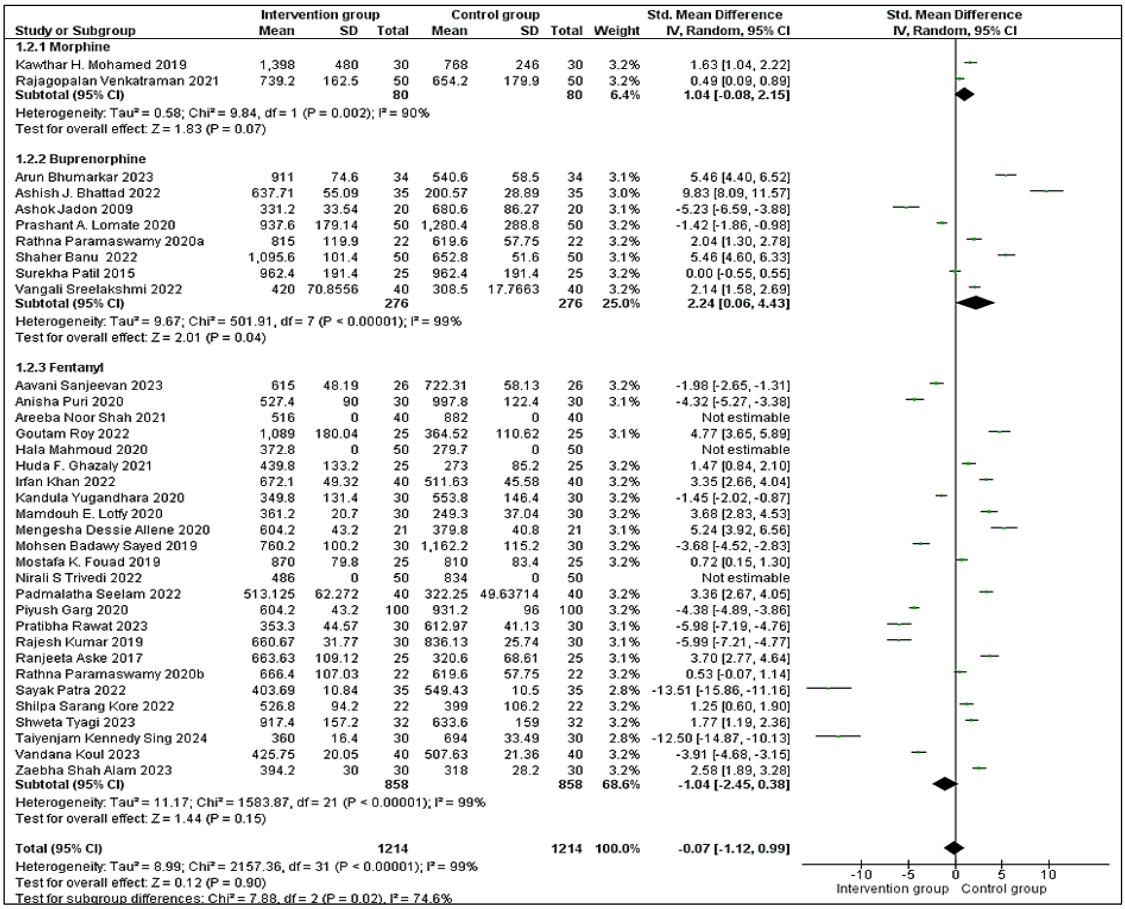

Figure 8: Forest Plot Doth Set Forth: The Findings of the Subgroup Research wherein the Several Analgesic Adjuvants are weighed in their Influence upon the Standardized Mean Difference of the Duration of Analgesia, Measured in Minutes

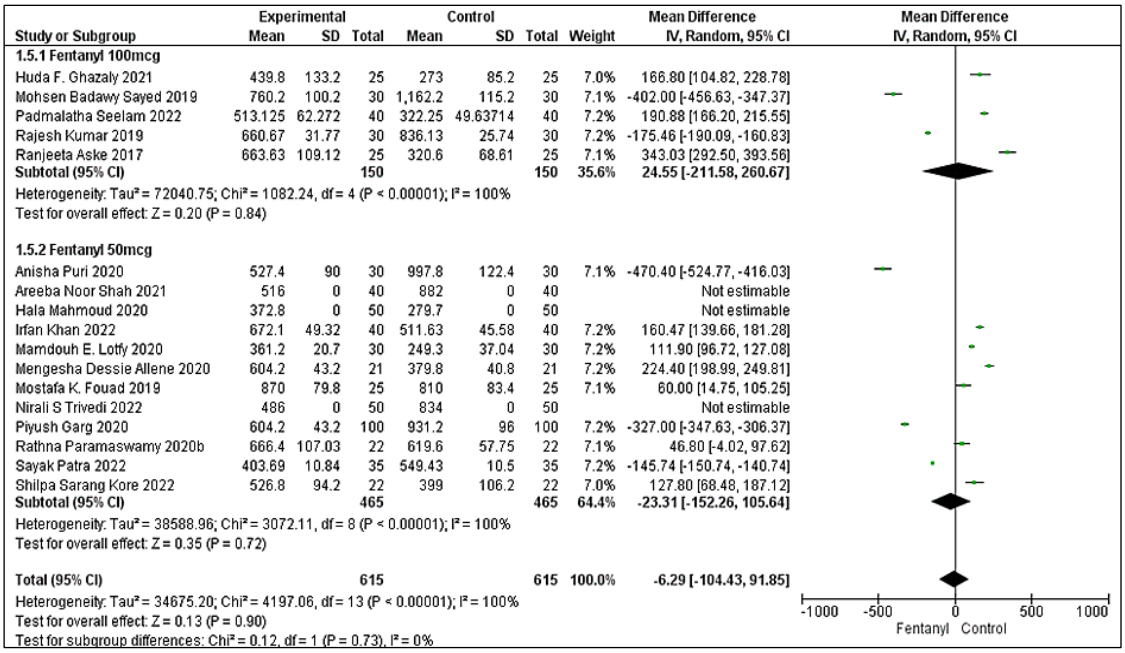

Figure 9: Forest Plot Presents Fentanyl Concentration–Based Subgroup Analysis of Postoperative Analgesia Duration, showing Standardized Mean Differences, Variability, and Heterogeneity across Studies

Across 39 studies (42 RCTs), opioid adjuvants significantly hastened sensory block onset, with buprenorphine showing the greatest effect, followed by fentanyl and morphine. Higher fentanyl doses (100 µg) shortened onset more than 50 µg. Overall postoperative analgesia duration showed no significant improvement versus controls, with substantial heterogeneity and several non-opioid adjuvants demonstrating comparable or superior effects.

Discussion

This study analysed the impact of adjuvants (morphine, buprenorphine, and fentanyl) combination with other anaesthetic adjuvants in BPB. The study found that these adjuvants greatly accelerated the initiation of sensory block. The strength of the evidence, across all outcomes examined, did range from most modest to lowly in quality, for it was shadowed by the spectres of bias, inconsistency, and indirectness, as well as by uncertain wanderings in the potencies of the opioids and the local anaesthetic drugs employed.

Further, the selection of BPB technique typically depends on the type of surgeries, which can impact the duration of pain relief at the surgical site. For instance, the interscalene approaches are often used for shoulder surgeries, whereas axillary blocks are more suitable for procedures on the hand and forearm. These variations in approach can contribute to varying outcomes and clinical heterogeneity.

Terkawi and his fellows did undertake a meta-analysis to examine techniques that might enhance thoracic paravertebral nerve blocks in the surgery of the breast; and it was therein discovered that the combination of fentanyl as an adjuvant, together with the fashioning of multilevel blocks, did greatly advance the easing of pain. Similarly, another study showed that combined fentanyl with bupivacaine not only reduced the time required for spinal anaesthesia onset but also extended its duration during lower limb surgeries compared to bupivacaine (51-53). However, the analgesic effectiveness of perineural fentanyl remains inconsistent, with some studies suggesting minimal or no significant impact when used in peripheral nerve blocks (54, 55).

The clinical importance of this meta-analysis stems from its complete evaluation the beneficial effects of morphine, fentanyl, and buprenorphine as adjuvants in brachial plexus blocks. While previous studies have explored individual adjuvants, to our knowledge, this analysis is one of the first systematic efforts to pool data from all the RCTs conducted and assess their comparative impacts of adjuvants like morphine, buprenorphine, and fentanyl combinations with others on onset of sensory block and duration of postoperative analgesia. From our analysis, the overall results did not demonstrate significant differences in the duration of post-operative analgesia among morphine, fentanyl, and buprenorphine combinations but exhibited significant difference in onset of sensory block, whereas the subgroup analyses revealed some interesting pattern. In the subgroup analysis of fentanyl based on concentration, it showed that 100 µg (P = 0.72) extend duration of analgesia than the 50µg fentanyl in the duration of analgesia, but the significance level was at P = 0.90.

These observations add to the existing literature and provide a clearer understanding of the varied effects of these adjuvants. By pooling data from RCTs and employing detailed subgroup analyses, our study offers valuable insights for clinical practice. However, these findings also underline the need for further research to validate these trends and explore their implications in different clinical approaches and patient populations.

The conceptual framework for the development of expectations, with specific emphasis on brachial plexus anaesthesia with opioid additives, has its foundation in the psychological and physiological processes that interact with the individual's perceptions of effectiveness and actual pain relief. The patient's expectations of pain relief can play an influential role in patients' satisfaction with the surgery or operation and the degree of pain experienced. The role of healthcare professionals can then play an integral part in creating the positive experience of pain relief with the use of morphine, fentanyl, or buprenorphine by creating the possibility of the creation of positive experience through the use of opioid additives.

First, we would want to recognize the importance of clearly outlining the theoretical and empirical insights that our work aims to provide. This meta-analysis summarizes the body of research and highlights the unique effects of fentanyl, morphine, and buprenorphine as adjuvants in brachial plexus blocks. Theoretically, our findings help clarify how

opioid adjuvants can improve anaesthetics outcomes and identify future research goals in the field. Empirically, they provide information required for the optimization of pain management strategies in upper limb procedures.

One major weakness of this systematic review and meta-analysis is the vast variation among the research, as the adjuvant pairings and dose measurements varied greatly from one work to the next. Additionally, differences in study protocols, such as the type of brachial plexus block, anaesthetic techniques, and the specific local anaesthetics' used in combination with our drug of interest morphine, buprenorphine, or fentanyl, which introduces heterogeneity that might impact the comparability of results. Less number of studies could be one of the limitations of the study and the concentrations of the anaesthesia and their combination limits the study outcome. Also, additional factors such as patient comorbidities, age, and the type of surgery might not have been consistently considered across studies, which could introduce some bias into the results. This variability further complicates our ability to generalise the findings.

Future work would likely involve standardizing procedures for morphine, buprenorphine, and fentanyl as additives in brachial plexus procedures, with a focus on standardizing dosage amounts and methods of delivery. Furthermore, work on the pharmacokinetic and pharmacodynamics profiles of said opioids in other varying patient groups, possibly with other comorbidities, could possibly provide some insight into optimal pain control strategies. Longitudinal research regarding long-term pain control as well as side effects of opioid medications could provide some benefit. Similarly, researching synergistic effects of above said opioids with other local anaesthetics, as well as other additives, could possibly improve pain control and patient satisfaction for upper extremity surgical procedures.

Conclusion

In summary, this meta-analysis shed important light on the effectiveness of morphine, buprenorphine, and fentanyl adjuvants in brachial plexus blocks performed in upper extremity surgery. From our data, we can conclude that, regardless of the opioid used, there was a profound decrease in the time to obtain a sensory block, (onset) but it did not affect the mean analgesic period (duration) in comparison to the groups that used alternative adjuvants. However, the buprenorphine opioid was found to have the most effective start time, potentially indicating its benefit over others in clinical practice. The sub-group analysis favoured the control group with other combinations which includes the Verapamil, dexmedetomidine, tramadol, dexamethasone, diclofenac, adrenaline, normal saline, hyaluronidase indicated similarity in duration of analgesia against combination with these opioids.

Although there are some drawbacks in this research concerning the heterogeneity of the studies, it clearly indicates that more research and more alternative adjuvants and opioids are needed to provide an effective strategy in this field, potentially extending and improving the outcomes of pain relief.

Abbreviations

None.

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Author Contributions

All authors have equally contributed to the manuscript including concept, design, data search, write up, supervision.

Conflict of Interest

No.

Declaration of Artificial Intelligence (AI) Assistance

AI has been used to correct language and rephrase a few sentences.

Ethics Approval

There are no ethical issues as the work is a systematic review.

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Supplementary Figure 1: Risk of Bias of Each Study -Cochrane Collaboration's Tool for Evaluating the Evidence Synthesis Risk of Bias (The Colours Represent Different Categories: Red- Equal High Bias, Green- Equal Low Bias, Yellow- Equal Unclear Bias)

Supplementary Table 1: Study Characteristics/ Details of Study Groups and Adjuvants Concentrations of Included RCTs

Studies	Drug of interest	Intervention group		Control Group	
		Name of the Adjuvants	Concentration Of Adjuvants	Name of the Adjuvants	Concentration Of Adjuvants
Venkatraman *et al*., 2021(12)	Morphine	Morphine Ropivacaine	50µg of morphine, 30 ml of 0.5% ropivacaine	Dexamethasone, ropivacaine	50µg of dexamethasone, 30 ml of 0.5% ropivacaine
Mohamed *et al*., 2019(13)	Morphine	Morphine Bupivacaine	24 ml bupivacaine 0.5%+5 mg morphine	Bupivacaine	24 ml bupivacaine 0.5%
Elmaghraby *et al*., 2021(14)	Morphine	Morphine Bupivacaine, Lidocaine	20 ml containing 9 ml bupivacaine 0.5%- and 9-ml lidocaine 2% + 5 mg morphine in 2 ml normal	Bupivacaine, lidocaine, normal saline	20 ml containing 9 ml bupivacaine 0.5%- and 9-ml lidocaine 2% plus 2 ml normal saline
Wang *et al*., 2017(15)	Morphine	Morphine Ropivacaine	24 ml (120 mg) of 0.5% ropivacaine plus 1 ml (2 mg) morphine	Ropivacaine, saline	24 ml (120 mg) of 0.5% ropivacaine plus 1 ml saline
Saryazdi *et al*., 2015(16)	Morphine	Morphine Lidocaine, epinephrine	40 ml of 1% lidocaine with epinephrine 1/200,000 concentration and 5 mg morphine injected	Pethidine, epinephrine	40 ml of 1% lidocaine with epinephrine 1/200,000 concentration and injected 50 mg pethidine
Banu *et al*., 2022(17)	Buprenorphine	Buprenorphine Ropivacaine	Inj. Ropivacaine 0.5%, 2mg/kg and Buprenorphine 6mcg/kg	Ropivacaine, Tramadol	inj. Ropivacaine 0.5%, 2mg/kg and Tramadol 2mg/kg
Sreelakshmi *et al*., 2022(18)	Buprenorphine	Buprenorphine Ligocaine, adrenaline	7mg/kg of 2% lignocaine with adrenaline (1:200000) +3µg/kg of buprenorphine	Lignocaine, adrenaline, dexmedetomidine	7mg/kg of 2% lignocaine with adrenaline (1 in 200000) + Dexmedetomidine (1µg/kg).
Jadon *et al*., 2009(19)	Buprenorphine	Buprenorphine Bupivacaine, saline	30 ml 0.3% bupivacaine+ 1 ml saline and intramuscular 1ml drug (3µgkg-1 buprenorphine + saline	Bupivacaine, saline	30 ml 0.3% bupivacaine + 1 ml study drug (3µg.kg-1 bupivacaine + saline to make volume= 1 ml)

			to make volume= 1 ml).		and 1 ml of intramuscular injection of saline.
Patil S, *et al.*, (2015) (20) Elmaghraby *et al.*,(2021) (14)	Buprenorphine	Buprenorphine, Bupivacaine, ligocaine, adrenaline, saline, hyaluronidase	20 ml 0.5% bupivacaine + 15 ml 2% lignocaine with adrenaline (1:200,000) + 4 ml normal saline + 1500 units hyaluronidase + 3 µg/kg buprenorphine diluted to 1 ml normal saline	Bupivacaine, lignocaine, adrenaline, normal saline, hyaluronidase	20 ml 0.5% bupivacaine + 15 ml 2% lignocaine with adrenaline (1:200,000) + 4 ml normal saline + 1500 units hyaluronidase + 1 ml normal saline.
Bhattad *et al.*, 2022(21)	Buprenorphine	Buprenorphine Ligocaine, adrenaline	30cc of 1% Lignocaine + Adrenaline 5mcg / ml (1:200000) containing 150mcg of Buprenorphine	Buprenorphine, lignocaine, adrenaline, verapamil	30cc of 1% Lignocaine + Adrenaline 5mcg / ml (1: 200000) containing 150mcg of Buprenorphine and 2.5mg of Verapamil
				Lignocaine, adrenaline	30cc of 1% Lignocaine + Adrenaline 5mcg/ml (1:200000)
Lomate *et al.*, 2020(22)	Buprenorphine	Buprenorphine bupivacaine, tramadol, dexamethasone, and diclofenac	150 µg buprenorphine plus tramadol 50 mg IV, dexamethasone 4 mg IV, and diclofenac 75 mg infusion	Bupivacaine, dexmedetomidine	50 µg dexmedetomidine, perineurally added to 30 ml of 0.375% bupivacaine, tramadol 50 mg IV, dexamethasone 4 mg IV, and diclofenac 75 mg
Bhumarkar *et al.*, 2023(23)	Buprenorphine	Buprenorphine Ropivacaine	30 ml 0.5% Ropivacaine + 0.3 mg 1 ml Buprenorphine	Ropivacaine, normal saline	30 ml 0.5% Ropivacaine + 1ml Normal saline
Paramaswamy *et al.*, 2020(24)	Buprenorphine	Buprenorphine Ropivacaine	20 ml of ropivacaine 0.5% and 300µg buprenorphine	Ropivacaine, saline	20 ml of ropivacaine 0.5% and 1ml of 0.9% saline

Saryazdi *et al*., 2015b(16)	Buprenorphine	Buprenorphine Lidocaine, epinephrine	40 ml of 1% lidocaine with epinephrine 1/200,000 concentration and 0.2 mg buprenorphine was injected.	Pethidine, Lidocaine, epinephrine	40 ml of 1% lidocaine with epinephrine 1/200,000 concentration and injected 50 mg pethidine
Aske *et al*., 2017(25)	Fentanyl	Fentanyl Bupivacaine, lignocaine, adrenaline	10 ml of Bupivacaine 0.5% (1 mg/kg) +2 ml Fentanyl (100 microgram) and 18 ml of 2% lignocaine with adrenaline	Bupivacaine, Lignocaine, adrenaline, normal saline	0 ml of 0.5% Bupivacaine (1 mg/kg) and 18 ml of 2% Lignocaine with adrenaline (7 mg 1 kg) + 2 ml normal saline
Kumar *et al*., 2019(26)	Fentanyl	Fentanyl Bupivacaine, saline	20 ml of 0.5% bupivacaine with 2 ml fentanyl 100 µgm with 10 ml of normal saline	Bupivacaine, nalbupine, normal saline	20 ml of 0.5% bupivacaine with 2 ml of nalbuphine 20 mg with 10 ml Normal Saline (NS)
Roy *et al*., 2022(27)	Fentanyl	Fentanyl Bupivacaine	0.4 ml/kg bupivacaineplus 1 mcg/kg fentanyl	Bupivacaine + normal saline	0.4 ml/kg bupivacaine up to a maximum of 30 ml volume plus 1ml of normal saline
Garg *et al*., 2020(28)	Fentanyl	Fentanyl Ropivacaine	0.5% Ropivacaine 30ml + fentanyl 50mcg (1ml)	Ropivacaine + tramadol	0.5% Ropivacaine 30ml + tramadol 50mg (1ml)
Puri *et al*., 2020(29)	Fentanyl	Fentanyl Bupivacaine, lignocaine, adrenaline, saline	10 ml of 0.5% bupivacaine + 20 ml of 2% lignocaine with adrenaline (1:200,000) and 1 µg/kg fentanyl diluted till 35 cc with normal saline	Bupivacaine, lignocaine, clonidine, normal saline	10 ml of 0.5% bupivacaine + 20 ml of 2% lignocaine with adrenaline (1:200,000) and 1 µg/kg clonidine diluted till 35 cc with normal saline
Shah *et al*., 2021(30)	Fentanyl	Fentanyl Ropivacaine	0.5% Ropivacaine 30ml + fentanyl 50mcg (1ml)	Ropivacaine, tramadol	0.5% Ropivacaine 30ml + tramadol 50mg (1ml)
Khan *et al*., 2022(31)	Fentanyl	Fentanyl Ropivacaine	30 ml of 0.5% ropivacaine with 50 µg fentanyl	Ropivacaine, magnesium sulfate	30 ml of 0.5% ropivacaine with 250 mg

					magnesium sulfate
Mahmoud *et al*., 2020(32)	Fentanyl	Fentanyl Levobupivacaine, saline	22.5ml levobupivacaine 0.5 % + 1ml Fentanyl (50µg) + 6.5ml normal saline	Levobupivacaine, normal saline	22.5ml levobupivacaine 0.5 % + 7.5ml normal saline
Patra *et al*., 2022(33)	Fentanyl	Fentanyl Bupivacaine	bupivacaine (0.5%) 29 ml with 50 µg (1 ml) of fentanyl	Bupivacaine, dexmedetomidine	bupivacaine (0.5%) 29 ml with 100 µg (1 ml) of dexmedetomidine
Allene *et al*., 2020(34)	Fentanyl	Fentanyl Bupivacaine	50 mg fentanyl þ 0.25% bupivacaine	Tramadol, bupivacaine Bupivacaine	100 mg tramadol þ 0.25% bupivacaine 0.25% bupivacaine
Kore *et al*., 2022(35)	Fentanyl	Fentanyl Bupivacaine, lignocaine	injection bupivacaine (0.5%) 20 cc + injection lignocaine (2%) 10 cc + injection fentanyl 50 µgm	Bupivacaine, lignocaine, saline Bupivacaine, lignocaine, dexamethasone	injection bupivacaine (0.5%) 20 cc + injection lignocaine (2%) 10 cc + injection 0.9% normal saline bupivacaine (0.5%) 20 cc + injection lignocaine (2%) 10 cc + injection dexamethasone 8 mg
Seelam *et al*., 2022(36)	Fentanyl	Fentanyl Ropivacaine	Fentanyl (100mcg) as an adjuvant to Ropivacaine (0.5%)	Ropivacaine	Ropivacaine 0.5%
Paramaswamy *et al*., 2020b(24) †	Fentanyl	Fentanyl Ropivacaine	20 ml of ropivacaine 0.5% and and 50 µg fentanyl	Ropivacaine, saline	20 ml of ropivacaine 0.5% and 1ml of 0.9% saline
Ghazaly *et al*., 2021(37)	Fentanyl	Fentanyl Bupivacaine, saline	20 ml of bupivacaine 0.5% plus fentanyl 100 µg in 2 ml	Bupivacaine, saline	20 ml bupivacaine 0.5% plus normal saline 2 ml
Fouad *et al*., 2019(38)	Fentanyl	Fentanyl Bupivacaine	Total volume of 30 ml bupivacaine 0.5% added to 50	Bupivacaine	30 ml bupivacaine 0.5%

			micrograms of fentanyl		
Koul *et al*., 2023(39)	Fentanyl	Fentanyl Bupivacaine	25 ml of 0.5% bupivacaine and 1µg/kg IBW of fentanyl	Bupivacaine, clonidine	0.5% bupivacaine with 1µg/kg of clonidine
Trivedi *et al*., 2022(40)	Fentanyl	Fentanyl Ropivacaine	0.5% Ropivacaine 30ml + fentanyl 50mcg (1ml)	Ropivacaine, tramadol	0.5% Ropivacaine 30ml + tramadol 50mg (1ml)
Sayed., 2019(41)	Fentanyl	Fentanyl Bupivacaine	100 mcg Fentanyl + 20 ml bupivacaine 0.5%. Total volume 22 ml	Bupivacaine, Dexamethasone	8mg dexamethasone + 20 ml of bupivacaine 0.5%. Total volume 22 m
Hossain *et al*., 2021(42)	Fentanyl	Fentanyl Bupivacaine	38 ml of 0.25% bupivacaine with 100 µg (2ml) of fentanyl to make a total volume of 40 ml	Bupivacaine, magnesium sulfate	38 ml of 0.25% bupivacaine with 80mg (2ml, 4%) magnesium sulfate
Lotfy *et al*., 2020(43)	Fentanyl	Fentanyl Bupivacaine	30 ml bupivacaine 0.5% with fentanyl 50 µg (1 ml)	Bupivacaine, Saline	30 ml 0.5% bupivacaine with 1 ml normal saline
Saryazdi *et al*., 2015c(16) †	Fentanyl	Fentanyl Lidocaine, epinephrine	40 ml of 1% lidocaine with epinephrine 1/200,000 concentration and 75 mcg Fentanyl was injected.	Pethidine, Lidocaine, epinephrine	40 ml of 1% lidocaine with epinephrine 1/200,000 concentration and injected 50 mg pethidine
Singh *et al*., 2024(44)	Fentanyl	Fentanyl Bupivacaine	0.5% inj bupivacaine(1.5mg/kg) with 1mcg/kg of inj.fentanyl	Bupivacaine, dexmedetomidine	0.5% inj bupivacaine (1.5mg/kg) with 1mcg/kg of inj. dexmedetomidine
Sanjeevan *et al*., 2023(45)	Fentanyl	Fentanyl Ropivacaine	ropivacaine 0.5% (20 ml)+Fentanyl 1 mcg/kg	Ropivacaine, dexmedetomidine	ropivacaine 0.5% (20 ml)+dexmedetomidine 1 mcg/kg and
Hashemi *et al*., 2021(46)	Fentanyl	Fentanyl Ropivacaine	ropivacaine (40 ml/0.5%) + fentanyl (1 µg/kg)	Ropivacaine, dexmedetomidine	ropivacaine (40 ml/0.5%) + dexmedetomidine (1 µg/kg)
Alam *et al*., 2023(47)	Fentanyl	Fentanyl Ropivacaine	28 cc of 0.75% Ropivacaine and	Ropivacaine, saline	28cc of 0.75% ropivacaine with

			fentanyl (1 mcg/kg)		2 ml NS. Total volume of 30 ml
Tyagi *et al*., 2023(48)	Fentanyl	Fentanyl Ropivacaine	0.5% Ropivacaine with 1mcg/kg Inj. Fentanyl to make 30 ml	Ropivacaine	0.5% Ropivacaine 30 ml
Rawat *et al*., 2023(49)	Fentanyl	Fentanyl Bupivacaine	15 ml inj. 0.25% bupivacaine + 1 µg/kg fentanyl	Bupivacaine, clonidine	15 ml Inj.0.25% bupivacaine + 1 µg/kg clonidine
				Bupivacaine, dexmedetomidine	15 ml Inj.0.25% bupivacaine + 1 µg/kg dexmedetomidine
Yugandhara *et al*., 2020(50)	Fentanyl	Fentanyl Lignocaine	0.5% lignocaine 40 ml + Fentanyl 0.1 mcg/kg	Lignocaine, tramadol	0.5% lignocaine 40 ml + Tramadol 1 mg/kg