

Intraoperative and Postoperative Effects of Dexmedetomidine as an Adjuvant to Bupivacaine in Transversus Abdominis Plane Block in Lower Abdominal Surgeries

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Abstract:

Background: Lower abdominal surgeries often result in severe pain, which in turn can affect the pattern of breathing and cause discomfort, irritation, and poor patient compliance. This investigation aimed to compare the analgesic efficacy of adding dexmedetomidine (DEX) as an adjuvant to bupivacaine in TAP block intraoperatively and postoperatively in lower abdominal surgeries. **Methods:** This prospective investigation included 60 cases undergoing lower abdominal surgery, randomly assigned into two equal groups. Group B received 40 mL of 0.25% bupivacaine (20 mL per side), while Group BD received 20 mL of 0.5% bupivacaine mixed with 0.5 mcg/kg DEX and diluted to 40 mL (20 mL per side) for TAP block. **Results:** NRS measurements at 2h, 4h, and 6h were statistically significantly diminished in Group BD in contrast with Group B ($P<0.001$). Time to first rescue analgesia was statistically significantly prolonged in Group BD. AEs were statistically insignificantly different between both groups. Degree of patient satisfaction (excellent) was statistically significantly elevated in Group BD in contrast with Group B ($P<0.001$). **Conclusion:** DEX integration into TAP block protocols represents a compelling strategy to enhance postoperative pain management characterized by extended duration, reduced rescue analgesic consumption, and diminish pain scores, particularly during the critical early recovery phase.

Keywords: Dexmedetomidine; Bupivacaine; Transversus Abdominis Plane Block; Lower abdominal Surgeries.

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Introduction

Postoperative pain associated with lower abdominal surgical interventions is often severe and may adversely impact respiratory function, manifesting as discomfort, restlessness, and reduced patient cooperation. Understandably, beyond apprehension regarding surgical outcomes, cases frequently identify postoperative pain as a principal concern⁽¹⁾. Persistent postoperative pain constitutes a substantial contributor to postoperative morbidity, diminished patient satisfaction, and prolonged hospitalization. Effective postoperative analgesia serves as a fundamental pillar in optimizing recovery and accelerating rehabilitation after lower abdominal procedures. Inadequate analgesic management has been consistently associated with suboptimal functional recovery. Furthermore, sustained nociceptive stimulation postoperatively may activate the hypothalamic-pituitary-adrenal (HPA) axis, leading to immunosuppression, which predisposes cases to surgical site infections and impaired wound healing. Additionally, inadequate pain control may result in limited ambulation, consequently increasing the risk of thromboembolic events such as pulmonary embolism, deep vein thrombosis, and respiratory complications including pneumonia⁽²⁾. The transversus abdominis plane (TAP) block is a refined regional anesthetic technique commonly utilized to deliver effective postoperative analgesia in abdominal surgery. It targets the sensory nerves innervating the anterolateral abdominal wall, which pass through the neurofascial plane situated between the internal oblique and transversus abdominis muscles. By administering local anesthetic (LA) into this defined space, superficial to the transversus abdominis, the block disrupts afferent nociceptive input, thereby achieving focused and reliable pain control.⁽³⁾

Although the TAP block alone does not offer complete anesthetic coverage for

intra-abdominal procedures, it represents an essential component of a multimodal analgesia (MMA) regimen. The widespread application of locoregional techniques, particularly utilizing bupivacaine, has been instrumental in minimizing perioperative opioid requirements and associated adverse effects. When administered as an adjunct to general anesthesia (GA), regional techniques such as the TAP block enhance postoperative analgesic efficacy, reduce the need for intra- and postoperative opioids, and subsequently diminish the incidence of opioid-related adverse events (AEs) postoperative recovery, earlier ambulation, and reduced duration of hospital stay⁽⁴⁾.

To further enhance the efficacy of regional anesthesia, adjuvant agents may be co-administered with local anesthetics. This approach aims to prolong analgesia, optimize block characteristics, and decrease local anesthetic toxicity. Among the pharmacologic adjuvants, dexmedetomidine (DEX) has shown promising results in improving block quality and duration⁽⁵⁾.

DEX is a precision-targeting α_2 -adrenergic receptor agonist, valued for its unique ability to blend sedation, analgesia, and sympatholysis, while concurrently reducing the need for additional anesthetic agents. Its efficacy as an adjuvant to LAs is primarily attributed to two peripheral mechanisms: (i) local vasoconstriction at the injection site, which delays systemic absorption of the anesthetic and prolongs its action; and (ii) direct modulation of peripheral nerve activity, enhancing the depth and duration of the block⁽⁶⁾.

The current investigation was undertaken to assess and compare the analgesic efficacy of bupivacaine alone versus bupivacaine combined with DEX for TAP blocks administered intraoperatively in cases undergoing lower abdominal surgery.

Patients and methods:

Patients:

This was a prospective, randomized, double-blind, controlled clinical trial conducted on 60 adult cases scheduled for elective lower abdominal surgery at Benha University Hospital. The investigation spanned a period of six months following the approval of the institutional Research Ethics Committee, Faculty of Medicine, Benha University. Informed written consent was obtained from all participants prior to enrollment. The study period is from June 2024 to June 2025.

Inclusion criteria were encompassed adult cases (>18 years), of both sexes, classified as American Society of Anesthesiologists (ASA) physical status I or II, and scheduled for lower abdominal surgery.

Exclusion criteria included patient refusal, known hypersensitivity to bupivacaine or DEX, history of chronic opioid therapy or substance abuse (e.g., benzodiazepines), psychiatric illness, seizure disorders, uncontrolled hypertension (HTN), advanced heart block, uncontrolled diabetes mellitus (DM), current use of anticoagulant therapy, hypothermia, or clinically significant acid-base disturbances.

Randomization and Group Allocation

This randomized controlled clinical investigation included a total of 60 participants who were scheduled for elective abdominal surgery under general anesthesia. To ensure unbiased group assignment and proper allocation concealment, a computer-generated randomization sequence was utilized. Participants were randomly and equally assigned to one of two groups, with 30 cases in each.

The first group, designated as Group B (Bupivacaine-only group), received a total of 40 mL of 0.25% bupivacaine administered via a bilateral TAP block. Each side of the abdomen was injected with 20 mL of the solution. The second group, referred to as Group BD (Bupivacaine + Dexmedetomidine group),

received a mixture comprising 20 mL of 0.5% bupivacaine combined with DEX at a dose of 0.5 mcg/kg. This mixture was diluted to achieve a total volume of 40 mL, with 20 mL administered on each side during the TAP block. This setup allowed for a direct comparison between the analgesic effects of bupivacaine alone and bupivacaine combined with DEX.

Methods:

All participants underwent thorough preoperative assessments to ensure they met the eligibility criteria and were adequately prepared for the planned surgical procedure. A comprehensive medical history was taken, which included demographic data such as age, sex, occupation, place of residence, level of education, and socioeconomic status. In addition, cases were asked about their smoking habits, the primary indication for surgery, and any personal or family history of chronic diseases, with particular attention paid to diabetes mellitus (DM) and hypertension (HTN).

Following history-taking, each patient received a detailed physical examination. Vital signs, including heart rate (HR), systolic and diastolic blood pressure (SBP and DBP), respiratory rate (RR), and peripheral oxygen saturation (SpO₂), were measured using standard non-invasive monitoring techniques. Baseline laboratory investigations were also conducted to evaluate each patient's general health status and suitability for surgery. These investigations included a complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and a coagulation profile encompassing prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR). Additional tests included serum electrolytes (sodium and potassium), fasting blood glucose levels, renal function tests (urea and creatinine), and liver function tests (AST, ALT, bilirubin).

On the day of surgery, all cases were monitored using standard ASA monitors.

A wide-bore intravenous (IV) cannula was inserted for medication administration. General anesthesia was induced using intravenous fentanyl at a dose of 1 mcg/kg, followed by propofol at 2 mg/kg to induce unconsciousness. Muscle relaxation was achieved with cisatracurium at a dose of 0.2 mg/kg. After confirming successful endotracheal intubation with capnographic waveform analysis, anesthesia was maintained with 1.5% isoflurane in oxygen. Additional doses of cisatracurium were administered intraoperatively based on the patient's neuromuscular monitoring. For intraoperative analgesia, intravenous pethidine was administered in titrated doses according to hemodynamic responses and patient needs.

Procedure:

After induction of general anesthesia and stabilization of the patient's vital parameters, a bilateral TAPs block was performed under ultrasound guidance using a lateral approach. Full aseptic precautions were observed throughout the procedure. A GE Logiq P7 ultrasound machine equipped with a 12 MHz linear probe (LA4-35) was utilized to identify the anatomical landmarks of the abdominal wall. The probe was positioned transversely along the midaxillary line, between the subcostal margin and the iliac crest, allowing for clear visualization of the three muscular layers: the external oblique, internal oblique, and transversus abdominis muscles.

Using an in-plane technique, a block needle was inserted approximately 1 cm medial to the probe at the level of the anterior axillary line. The needle was advanced under real-time ultrasound visualization into the fascial plane between the internal oblique and transversus abdominis muscles. Once the needle tip was accurately placed and negative aspiration was confirmed to avoid vascular puncture, the assigned anesthetic solution was injected slowly. In Group B, cases received 20 mL of 0.25% bupivacaine per side, totaling 40 mL. In contrast, cases in

Group BD received 20 mL of a solution containing 0.5% bupivacaine with 0.5 mcg/kg dexmedetomidine, also totaling 40 mL (20 mL per side). The distribution of the injectate was visualized in real-time to ensure proper spread within the targeted plane.

The duration of each surgical procedure was documented in minutes. All TAP blocks were administered by an experienced anesthesiologist trained in ultrasound-guided regional anesthesia to ensure consistency and accuracy of the technique.

Approval code: MS 20-5-2024

Statistical analysis

All statistical procedures were executed using the Statistical Package for the Social Sciences (SPSS), version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were exhibited as mean values with their corresponding standard deviations (SD), capturing the central tendency and variability within each group. To compare these continuous measures between groups, the unpaired Student's *T*-test was employed, offering a robust assessment of mean differences. Categorical variables, on the other hand, were presented as absolute frequencies and relative percentages, with intergroup comparisons analyzed using either the Chi-square (χ^2) test or Fisher's exact test, depending on data distribution and expected cell counts. Throughout the analysis, a *P*-value less than 0.05 was deemed statistically significant, reflecting a threshold of evidence sufficient to reject the null hypothesis and suggest meaningful group differences.

Results:

Demographic variables exhibited comparability between the two groups.

Table 1.

Total pethidine consumption during both the intraoperative period and the first 12 postoperative h was significantly diminished in Group BD in contrast with

Group B ($P = 0.008$ and $P < 0.001$, respectively). **Table 2**

HR measurements at 0 and 12 h postoperatively exhibited comparability between the groups; however, HR values recorded at 2, 4, and 6 h were significantly reduced in Group BD in contrast with Group B ($P < 0.001$). Similarly, MAP at baseline and at 12 h postoperatively exhibited comparability between the groups, whereas MAP values at 2, 4, and 6 h were significantly diminished in Group BD ($P < 0.001$). **Figure 1**

NRS scores for pain at 0 and 12 h also exhibited comparability between the groups, while significantly diminished

NRS scores were recorded in Group BD at 2, 4, and 6 h postoperatively ($P < 0.001$).

Table 3

Furthermore, the time to first request for rescue analgesia was significantly extended in Group BD (7.66 ± 0.47 h) in contrast with Group B (4.4 ± 0.49 h).

Table 4.

The incidence of AEs exhibited comparability between both groups. Notably, the proportion of cases reporting an "excellent" level of satisfaction was significantly elevated in Group BD (90%) as opposed to Group B (0%) ($P < 0.001$).

Table 5

Table 1: Demographic data of the studied groups

		Group B (n=30)	Group BD (n=30)	P value
Age (years)	Mean \pm SD	34.93 \pm 8.88	37.5 \pm 11.45	0.336
Sex	Male	18(60%)	20(66.66%)	0.788
	Female	12(40%)	10(33.33%)	
ASA classification	ASA I	25(83.33%)	20(66.66%)	0.233
	ASA II	5(16.66%)	10(33.33%)	
Duration of surgery (min)	Mean \pm SD	122.83 \pm 17.94	119.83 \pm 17.83	0.518

ASA: American Society of Anaesthesiologists

Table 2: Total Pethidine consumption (mg) of the studied groups

		Group B(n=30)	Group BD (n=30)	P value
Intraoperative		18(60%)	7(23.33%)	0.008*
Postoperative in 1 st 12h	Mean \pm SD	86.66 \pm 34.574	50 \pm 0	<0.001*

*: statistically significant as P value <0.05

Table 3: NRS measurements of the studied groups

	Group B (n=30)	Group BD (n=30)	P value
0h	1(0-1)	0(0-1)	0.198
2h	3(3-4)	1(1-2)	<0.001*
4h	4(3-4)	2(1-2)	<0.001*
6h	5(4-5)	2(1-2)	<0.001*
12h	3(2-3)	2(2-3)	0.191

*: statistically significant as P value <0.05, NRS: Numeric Pain Rating Scale, Data are presented as Median (IQR)

Table 4: Time to first rescue analgesia (h) of the studied groups

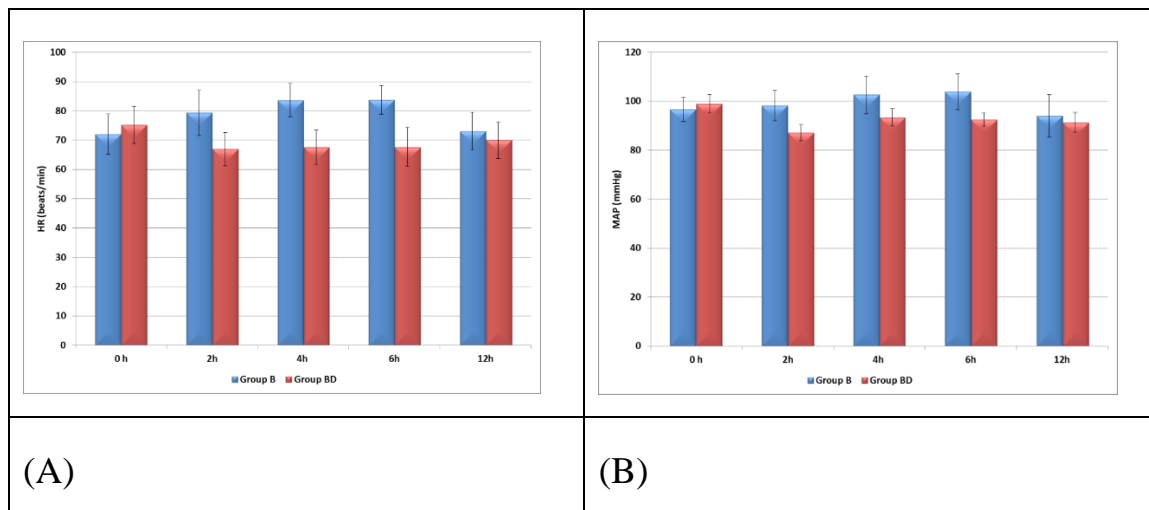
		Group B (n=30)	Group BD (n=30)	P value
Time to first rescue analgesia (h)	Mean \pm SD	4.4 \pm 0.49	7.66 \pm 0.47	<0.001*

*: statistically significant as P value <0.05

Table 5: Adverse events and degree of patient satisfaction of the studied groups

		Group B (n=30)	Group BD (n=30)	P value
Hypotension		2(6.67%)	0(0%)	0.150
Bradycardia		0(0%)	1(3.33%)	0.315
PONV		2(6.67%)	0(0%)	0.150
LAST		0(0%)	0(0%)	1
Total adverse events		4(13.33%)	1(3.33%)	0.161
Degree of patient satisfaction	Excellent	0(0%)	27(90%)	<0.001*
	Good	13(43.33%)	3(10%)	0.008*
	Fair	17(56.66%)	0(0%)	<0.001*

LAST: Local anesthetic systemic toxicity. PONV: Postoperative Nausea and Vomiting. *Significant as P value \leq 0.05.

**Figure 1:** (A) HR and (B) MAP measurements of the studied groups.

Discussion:

The findings of the current investigation indicate that the addition of DEX to bupivacaine significantly enhances intraoperative analgesia. In the group receiving the combination (Group BD), only 23.33% of cases required supplemental opioid administration, in contrast with 60% in the bupivacaine-only group (Group B). This notable reduction highlights the opioid-sparing effect of DEX and supports its role in improving perioperative pain management. By minimizing the need for intraoperative opioid use, the combination also reduces the risk of opioid-related side effects, contributing to a safer and more comfortable surgical experience.

These results are consistent with those exhibited by Madangopal and co-authors

⁽⁷⁾ who conducted a randomized, triple-blind trial in cases undergoing inguinal hernioplasty. Their investigation demonstrated that the addition of DEX, particularly at a dose of 0.5 mcg/kg, significantly prolonged the duration of postoperative analgesia. Cases receiving this dose experienced a mean pain-free period of approximately 874 minutes, in contrast with 341.5 minutes in the controls. Furthermore, the total consumption of postoperative analgesics was significantly lower in the DEX group. Although mild sedation and transient hemodynamic changes were observed, these effects were clinically manageable. Overall, the evidence strongly supports the use of DEX as an effective adjuvant for enhancing the quality and duration of regional anesthesia⁽⁷⁾

In the critical first 12 h following surgery, effective pain control plays a critical role in shaping patient comfort and recovery trajectory. In our investigation, cases in the BD group demonstrated markedly reduced opioid requirements, with a mean pethidine consumption of just 50 mg, lower than the 86.66 mg recorded in the B group. This significant reduction highlights the enhanced analgesic efficacy of the BD combination, showcasing its opioid-sparing capacity and its potential to mitigate opioid-related AEs such as nausea, sedation, and delayed mobilization.

These findings are consistent with the investigation by Almarakbi and Kaki⁽⁸⁾ who investigated the same adjuvant strategy in 50 patients undergoing TAH. Their DB design compared a standard TAP block using B alone with a block augmented by 0.5 µg/kg DEX. The results were compelling: the DEX group experienced a significantly longer pain-free interval (470 min vs. 280 min; $P < 0.001$) and a notable reduction in 24 h morphine consumption (19 mg vs. 29 mg; $P < 0.001$). This evidence reinforces the conclusion that DEX not only extends the duration of analgesia but also reduces total opioid burden in the postoperative period⁽⁸⁾.

In addition to its analgesic benefits, DEX conferred superior HD stability in the early postoperative phase. Although HR and BP were statistically comparable between groups at baseline and at 12 h, significant differences emerged at 2 h, 4 h, and 6 h postoperatively. The BD group showed consistently lower mean HR and BP during these intervals, reflecting the sympatholytic and vagomimetic effects of DEX. By modulating autonomic tone, DEX contributes to a calmer hemodynamic profile, an effect that may be particularly advantageous in patients at risk for CV fluctuations.

Collectively, these findings underscore the multidimensional value of DEX as an adjunct: prolonging analgesia, minimizing

opioid reliance, and enhancing perioperative physiological stability, all without a corresponding increase in AEs. As the pursuit of effective, opioid-sparing, multimodal analgesia continues to evolve, DEX emerges as a key player in redefining regional anesthesia strategies.

In contrast to the significant intermediate alterations in hemodynamics observed in our BD group, Qian and co-authors⁽⁹⁾ reported notably different outcomes in their RCT involving 70 C/S patients¹. Their trial compared TAP blocks using 0.3% R alone (Group R) versus R combined with 0.5 µg/kg DEX (Group RD). Despite evaluating HR and BP across multiple postoperative intervals, specifically at 2, 4, 6, 8, 10, 12, and 24 h, they found comparability between the two groups ($P > 0.05$). Furthermore, none of the patients experienced hypotension or bradycardia, suggesting a stable cardiovascular profile throughout the observation period. This contrasts with our findings, where the BD group exhibited consistently lower mean HR and BP at 2, 4, and 6 h in contrast with the B group, reflecting the sympatholytic and vagomimetic effects of DEX. While these changes were transient and clinically manageable, they emphasize the physiological influence DEX can exert on early postoperative hemodynamic⁽⁹⁾.

Parallel to these hemodynamic findings, the analgesic superiority of DEX was clear in our cohort when assessed via the NRS. Although scores at baseline (0 h) and late-phase (12 h) were similar between groups, the early-to-intermediate recovery period revealed significant differences. Median NRS scores in the BD group were markedly reduced at 2 h [1 (IQR 1–2) vs. 3 (IQR 3–4)], 4 h [2 (IQR 1–2) vs. 4 (IQR 3–4)], and 6 h [2 (IQR 1–2) vs. 5 (IQR 4–5)], when compared with the B group. These reductions highlight the rapid onset and sustained efficacy of DEX in enhancing analgesic coverage during the most critical phase of postoperative recovery, when pain intensity typically

peaks and patient discomfort is at its highest.

Supporting these findings, Mishra and co-authors⁽¹⁰⁾ conducted a similar investigation assessing the impact of adding DEX to R for TAP blocks in lower abdominal procedures. Patients receiving DEX (Group 2) demonstrated significantly lower VAS scores in contrast with those given R alone (Group 1), with statistically meaningful differences noted as early as 1 h ($P = 0.014$) and 3 h ($P = 0.027$) postoperatively. More importantly, this analgesic advantage persisted well into the later postoperative period, with reduced scores continuing at 12 h ($P = 0.011$) and 18 h ($P = 0.041$), underscoring the extended duration of pain relief associated with DEX.⁽¹⁰⁾

Consistent with these results, the current investigation demonstrated a prolonged pain-free interval in the BD group. The mean duration of effective analgesia, defined as the time to first request for rescue medication, was significantly longer in the BD group (7.66 ± 0.47 h) in contrast with the B group (4.4 ± 0.49 h). This 3-hour extension not only reinforces the analgesic constructive interaction between B and DEX but also reflects the clinical value of incorporating DEX into regional techniques for improving early recovery quality, reducing analgesic demand, and enhancing overall patient experience.

These findings are well supported by existing literature. Bansal and Sood⁽¹¹⁾ evaluated the impact of DEX added to ropivacaine in TAP blocks following cesarean delivery. Their results mirrored those of the present investigation, with the DEX group demonstrating a significantly longer time to first pain perception (6.6 ± 2.01 h vs. 5.03 ± 1.34 h; $P < 0.01$) and, importantly, a delayed need for rescue analgesia (7.8 ± 2.29 h vs. 6.47 ± 1.22 h; $P < 0.05$). These outcomes reinforce the role of DEX in extending the duration of regional anesthetic effects and reducing reliance on supplemental opioids.⁽¹¹⁾

Further evidence is provided by the work of Parameswari and Udayakumar, who compared bupivacaine alone with bupivacaine plus DEX for postoperative analgesia in cesarean section cases ($n = 35$ per group). Their investigation revealed significantly lower pain scores at multiple time points (4, 8, 12, 18, and 24 h) in the DEX group ($P = 0.046$), along with a marked prolongation in the time to first opioid administration (14.25 h vs. 7.73 h; $P = 0.0136$). In addition, the total opioid requirement over 24 h was dramatically reduced in the DEX group, with cases receiving a mean of only 11.43 mg of tramadol, in contrast with 32.86 mg in the controls ($P < 0.001$). Notably, these analgesic benefits were achieved without an associated rise in nausea or vomiting, although mild sedation (Ramsay score 3 vs. 2) was observed in some DEX recipients⁽¹²⁾.

From a safety standpoint, the current investigation observed comparable incidence of common AEs between groups. Events such as hypotension, bradycardia, and PONV occurred at comparable rates. Overall, AEs were exhibited in 13.33% of cases in Group B and 3.33% in Group BD, a difference that did not reach statistical significance. Importantly, no cases of LAST were identified in either group, further supporting the favorable safety profile of DEX when used within recommended dosing parameters.

Additional support for the safety profile of DEX as an adjuvant comes from the investigation by Varshney and co-authors⁽¹³⁾ who evaluated postoperative AEs in 90 healthy women undergoing CS under spinal anesthesia⁽¹³⁾. Participants were randomly placed into three distinct groups: Group C, which skipped the TAP block entirely; Group L, where they got a bilateral TAP block with a gentle dose of 0.25% levobupivacaine; and Group LD, where the same TAP block was given a boost with 1 μ g/kg of DEX. The findings demonstrated minimal side effects

associated with DEX. Notably, no cases of vomiting were detected in any group. Nausea incidence was identical in both the L and LD groups (2 cases each), while pruritus occurred slightly less frequently in the DEX group (1 in LD vs. 2 in L). Importantly, despite the relatively high DEX dose, none of the cases exhibited excessive sedation, as all maintained a Ramsay Sedation Score of 2, indicating calm wakefulness without drowsiness⁽¹³⁾. While AEs were similar across groups, patient satisfaction sharply diverged. An overwhelming 90% of cases who received DEX exhibited “Excellent” satisfaction, in contrast with 0% in the bupivacaine-only group. In contrast, 43.33% of cases in the bupivacaine group exhibited only “Good” satisfaction, while the remaining 56.66% rated their experience as “Fair.” These findings strongly suggest that the prolonged analgesic effect provided by the DEX combination contributes to a significantly improved patient experience, without an accompanying rise in common side effects.

This trend aligns with findings from Qian and co-authors⁽⁹⁾ who demonstrated that cases receiving DEX in combination with ropivacaine exhibited significantly elevated satisfaction scores during the first 48 h postoperatively, in contrast with those treated with ropivacaine alone⁽⁹⁾.

The consistent improvement in satisfaction underscores DEX’s value not only in pain relief but also in enhancing patient-centered outcomes.

Nevertheless, several limitations of the present investigation must be acknowledged. The single-center design, conducted at Benha University Hospital, may constrain the generalizability of the results to broader healthcare settings with different patient populations or clinical protocols. The small sample size (n = 60, 30 per group) may also limit the statistical power to detect more nuanced or rare effects. Furthermore, the follow-up period was confined to the first 24 postoperative h, potentially overlooking delayed-onset

AEs or long-term analgesic efficacy. Larger, multicenter trials with extended follow-up are needed to confirm and expand upon these findings

Conclusion:

DEX integration into TAP block protocols represents a compelling strategy to enhance postoperative pain management characterized by extended duration, reduced rescue analgesic consumption, and diminish pain scores, particularly during the critical early recovery phase.

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Author Contributions

Authors contributed equally and collaboratively to the entirety of this work. From the initial conceptual framework and investigation design to data collection, analysis, and critical interpretation, each author played an integral role. All authors were actively involved in drafting and refining the manuscript, have reviewed and approved the definitive version, and collectively accept full responsibility for the content and conclusions presented herein.

Conflicts of Interest

Authors affirm that there are no financial, personal, or professional conflicts of interest that could be perceived as influencing the investigation, authorship, or publication of this investigation. This declaration reflects a shared commitment to transparency, objectivity, and the ethical standards of scientific inquiry.

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