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Review Article

Anaesthesia Section

Dexmedetomidine as an Adjuvant to Local Anaesthetic Agents in Peripheral Nerve Blocks: A Review

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ABSTRACT

Peripheral Nerve Blocks (PNBs) are widely used for postoperative pain management. PNBs can improve postoperative recovery time and decrease the use of opiates after surgery. PNBs with Local Anaesthetics (LAs) alone last only a few hours. Adjuvants are medications that can be added to LAs to prolong the duration of PNBs. Dexmedetomidine (DEX) is one such adjuvant that has been studied extensively in PNBs. The aim of this review was to present an up-to-date literature on the use of DEX in various PNBs.

Keywords: Adjunct, Pain management, Post-op-analgesia

INTRODUCTION

Peripheral Nerve Blocks (PNBs) have become a cornerstone in various day surgeries and for postoperative pain management [1,2]. PNBs offer several advantages over conventional analgesics for postoperative pain management including quicker recovery after surgery and sparing the use of medications like opiates [3-6]. Analgesia from PNBs with Local Anaesthetic agents (LAs) lasts only a few hours. Increasing the dose of LAs may prolong the duration of analgesia, but it increases the risk of systemic toxicity [7,8]. Similarly, continuous infusion of LAs via a catheter allows for sustained analgesia but is limited by issues related to patient ambulation, catheter displacement, and risk of infection [9]. One-way to potentiate the effect of LAs in PNBs is the use of adjuvants [10]. DEX is an α-2 adrenoreceptor agonist that is commonly used as an adjuvant. Various studies have reported the use of DEX as an adjuvant in PNBs but they have small sample sizes and are done for different types of surgeries. The purpose of this review was to summarize the current literature on DEX as an adjuvant in various PNBs.

Literature Search

PubMed, Google Scholar and Web of Science were searched for relevant articles in English language reported till 31st May 2018. Articles published in non-English languages were not considered for inclusion. The following key words were used by themselves and in various combinations to search the literature: Dexmedetomidine, Precedex, adjuvant, adjunct, peripheral nerve blocks and names of individual nerve blocks. Bibliography of relevant articles was searched to identify additional articles of interest that were not found during initial literature search. When a meta-analysis for a PNB was found, individual studies done after the meta-analysis were discussed to present up to date information.

Terminology

Dexmedetomidine has been referred to as DEX in the entire manuscript. The phrase "…DEX added to Ropivacaine or Bupivacaine…" was used to reflect that the study compared the LA agent alone with the specified dose(s) of DEX to prevent complex sentence structures. Study groups that received DEX combined with Ropivacaine, Bupivacaine and Lidocaine were referred to as DEX-R, DEX-B and DEX-L, respectively.

Rationale for use of DEX

Perineural DEX acts by blockade of the hyperpolarization-activated cation current or I_h current. The I_h current brings a neuron back to the resting potential from the hyperpolarized state that follows an action potential. By blocking the I_h current, DEX causes prolonged hyperpolarization of the nerve, thereby delaying the restoration of resting potential and preventing the conduction of a new action potential [11]. This effect seems to be more pronounced in the unmyelinated C fibers (pain) than in A fibers (motor). Therefore, DEX produces better analgesia than muscle paralysis [12].

Studies have shown that LAs can lead to neurotoxicity in animal models and humans [13-15]. However, animal studies showed that addition of 20 mcg/kg of DEX had a protective effect against the neurotoxic effect of LAs [16,17]. Perineural DEX may reduce neurotoxicity by preventing translocation of NF-κB into the nucleus and decreasing the subsequent expression of inflammatory mediators like IL-6 and TNF-α [18].

Dosing of DEX

Different studies have shown that when used as an adjuvant to LAs, DEX provided adequate analgesia in doses varying from 20 mcg to 2 mcg/kg. Keplinger M et al., showed that DEX in 50, 100 and 150 mcg dose increased the duration of sensory block by 60, 72 and 57% respectively as compared to Ropivacaine alone ($p<0.05$). However, the use of 150 mcg DEX caused adverse events like deep sedation or post-block paresthesia in one-third of the patients [19]. Similarly, Abdulatif M et al., reported that addition of 25 mcg of DEX did not make any difference in the pharmacodynamics of Femoral Nerve Block (FNB) noted with Bupivacaine alone ($p>0.05$). Addition of 50 and 75 mcg of DEX were associated with a decrease in time to onset of sensory block and motor block, decrease in postoperative morphine consumption, and increase in duration of sensory block, motor block and time to first request of morphine ($p<0.05$). The 75 mcg of DEX was associated with increased incidence of pre- and intraoperative hypotension episodes ($p=0.002$) [20]. In a meta-analysis of 34 studies on Brachial Plexus Block (BPB), Vorobeichik L et al., concluded that 50-60 mcg of DEX maximised sensory block duration (52% increase in sensory block duration) with no hemodynamic side effects [3].

Route of Administering DEX

In most of the studies, DEX was mixed with LAs and given as a part of the block. However, Marhofer D et al., studied addition of 20 mcg of IV or perineural DEX to 22.5 mg Ropivacaine for Ulnar Nerve Block (UNB) in 36 volunteers. They showed that addition of either IV or Perineural DEX to Ropivacaine increased the duration of sensory, motor block and time until complete return of pinprick sensation ($p<0.05$). Perineural DEX had longer duration of sensory and motor block, and time until complete return of pinprick sensation as compared to IV DEX ($p<0.05$) [21]. Therefore, perineural administration of DEX is better than IV DEX in PNBs and should be the preferred route.

LIMITATION

a. Adverse events

Two separate meta-analyses on Brachial Plexus Block (BPB) showed that addition of DEX to LAs increased the odds of bradycardia (OR of 3.3-8.25), hypotension (5.4-5.62) and excessive postoperative sedation (OR of 17.2-19.67). There was no change in the occurrence of PONV or hypoxemia with the addition of DEX [3,22]. Vorobeichik L et al., also stated that DEX related bradycardia and hypotension were transient and did not require any intervention [3].

b. Cost

Another limitation of DEX is the cost. The cost of adding DEX to LAs has to be weighed against the benefits of DEX including decreased postoperative opiate use and early discharge from the hospital [3-6]. A formal cost effectiveness analysis needs to be conducted to determine if the benefits of adding DEX to LAs for PNBs can justify the cost of using it.

Role of DEX in Different Peripheral Nerve Blocks

1. Brachial plexus block: Vorobeichik L et al., performed a meta-analysis of 34 Randomised Controlled Trials (RCTs, n=2,007) comparing DEX (10-150 mcg or 0.75-1 mcg/ kg) with LAs to LAs alone in BPB. They showed that adding DEX to LAs increased the motor block duration by 61% and duration of analgesia by 69%. Addition of DEX to LAs decreased motor block onset time by 35%, sensory block onset time by 44%, mean morphine consumption in 24 hour after surgery by 11.6 mg, and reduced postoperative pain score at 24 hour by 0.5 on a standard VAS ranging from 0-10 [3]. A meta-analysis by Ping Y et al., included 18 RCTs (n=1,014) on addition of DEX (50-100 mcg) to LAs in BPB. They showed an increase in mean sensory block duration by 257 minutes, mean motor block by 242 minutes and mean time to first demand of analgesia by 266 minutes. The meta-analysis estimated that mean prolongation of sensory block was 282.65 minutes with long-acting LAs (Bupivacaine, Levobupivicaine and Ropivacaine) and 60.16 minutes with intermediate-acting LAs (Mepivacaine, Lidocaine), although the authors were concerned about bias in the estimate for intermediate acting LAs due to small number of studies available [22]. Hussain N et al., conducted a similar meta-analysis on 18 studies (n=1,092) and reported a reduction in onset of sensory (3.19 min) and motor (2.92 min) block, and increase in the duration of sensory (261.41 min) and motor (200.9 min) block, and duration of analgesia (289.31 min) with the addition of DEX to LAs. There was an increased incidence of intraoperative bradycardia (Risk difference 0.06) with of DEX [23].

Individual studies reported between June 2016 and May 2018 is summarised in [Table/Fig-1] [22,24-32]. All of these studies showed that addition of DEX to LAs improved one or more parameters of the BPB except the study done by Aksu R et al., That study did not find any difference in the parameters of supraclavicular block after addition of DEX to Bupivacaine [24]. This is most likely because the DEX group received only half the dose of Bupivacaine (50 mg) as compared to control group (100 mg).

Author and Year	Type of surgery	Type of block	Study groups (n)	Statistically significant results	Statistically significant adverse events
Rashmi et al., (25), 2017	Elective upper limb orthopedic surgery	Interscalene	Ropivacaine 225 mg alone or R (30) 50 mcg DEX-R or D (30)	1. Duration of sensory and motor block, and analgesia D>R 2. Onset of sensory or motor block D<R	None
Nazir et al., (26), 2016	Elective upper limb surgery	Supraclavicular	Bupivacaine 97.5 mg alone or B (35) 1 mcg/ kg DEX-B or D (35)	1. Duration of sensory and motor block, and analgesia D>B 2. Onset of sensory or motor block D<B	None
Thakur et al., (27), 2017	Elective forearm surgery	Axillary	Lignocaine 46 mg alone or Ln (30) 0.5 mcg/ kg DEX-Ln or D1 (30) 1 mcg/ kg DEX-Ln or D2 (30)	1. Duration of sensory and motor block, and analgesia D2>D1>Ln 2. Onset of motor and sensory block D2=D1>Ln 3. Use of IV analgesia D3=D2=D1=R 4. Time to IV analgesia D2>D1>R	None
Aksu et al., (24), 2017	Elective upper limb surgery	Supraclavicular	Bupivacaine 100 mg alone or B (25) 1 mcg/ kg DEX-B or D (25)	No difference in onset of sensory or motor block, duration of analgesia, duration of sensory or motor block, or patient satisfaction scores.	Bradycardia and dry mouth D>B
Farooq et al., (28), 2017	Elective upper limb orthopedic surgery	Supraclavicular	3 mg/kg of 0.75% Ropivacaine or R (35) 1 mcg/ kg DEX-R or D (35) 1 mcg/ kg Fentanyl-R or F (35)	1. Duration of sensory and motor block, and analgesia F>D>R 2. Onset of sensory or motor block F<D<R 3. Time to first IV analgesia F>D>R 4. Pain score up to 8 h post-op F=D<R	None
Bisui et al., (29), 2017	Elective upper limb surgery	Supraclavicular	Levobupivacaine 140 mg alone or LB (34) 0.75 mcg/ kg DEX-LB or D (33)	1. Duration of sensory and motor block, and analgesia D>LB 2. Onset of sensory or motor block D<LB 3. VAS at the time of IV analgesia D<M<R	HR and MAP up to 8 hours post-op D<LB
Koraki et al., (30), 2018	Elective forearm and hand surgery	Axillary	Ropivacaine 75 mg alone or R (n=18) 100 mcg DEX-R or D (n=19)	1. Duration of sensory and motor block, and analgesia D>R 2. Onset of sensory block D<R 3. Onset of motor block D=R	None
Elyazed et al., (31), 2018	Elective surgery of hand, wrist and forearm	Infraclavicular	Ropivacaine 175 mg alone or R (35) 100 mcg DEX-R or D (35) 150 mg Magnesium Sulfate-R or M (35)	1. Duration of sensory and motor block, and analgesia D>M>R 2. Onset of sensory or motor block D<M=R 3. Use of rescue analgesia D>M>R 4. 12-h post-op VAS D<M<R 5. Patient satisfaction D=M>R	Intra-op HR, MAP D<M=R
Jung et al., (32), 2018	Elective shoulder arthroscopy	Interscalene	Ropivacaine 100 mg alone or R (23) 1 mcg/ kg DEX-R or D1 (25) 1.5 mcg/ kg DEX-R or D2 (25) 2 mcg/ kg DEX-R or D3 (24)	1. Duration of sensory and motor block D3=D2=D1>R 2. Duration of analgesia D3>D2=D1>R 3. Use of IV analgesia D3=D2=D1=R	Perioperative hypotension D3=D2>D1=R

[Table/Fig-1]: Double blind randomised controlled trials on Brachial plexus block conducted after the meta-analysis by Ping Y et al., [22].

2. Cervical plexus block (CPB): DEX has been studied as an adjuvant to LAs for CPB in three separate studies [Table/Fig-2] [33-35]. Although the three studies differed in terms of their end points, they all showed beneficial effects of adding DEX to LAs. Only one study showed increased sedation, hypotension and bradycardia after surgery with DEX.

3. Ulnar nerve block: Keplinger M et al., compared 3 different doses of DEX with 22.5 mg Ropivacaine to Ropivacaine alone for UNB in 24 volunteers. Addition of 50, 100 and 150 mcg of DEX increased the mean sensory (8.5, 9.1, 8.3 h vs. 5.3 h; p<0.0001) and motor block (9.9, 11.8, 10.4 h vs. 4.9 h; p<0.0001) duration as compared to Ropivacaine alone, respectively. They also showed that increasing the dose of DEX increased the frequency of post-block sedation and paresthesia [19]. In another study, Marhofer D et al., compared 20 mcg of perineural or IV DEX with 22.5 mg of Ropivacaine to Ropivacaine alone for UNB in 36 volunteers. Addition of perineural or IV DEX to Ropivacaine increased the mean duration of sensory (555, 395 min vs. 350 min; p<0.05) and motor block (590, 438 min vs. 348 min; p<0.05), and mean time until complete return of pinprick sensation (743, 518 min vs. 455 min). The mean duration of sensory and motor block, and mean time until complete return of pinprick sensation in perineural DEX-R group was greater than in IV DEX-R group (p<0.05). IV DEX-R group had a faster mean onset of motor block (21 min) as compared to perineural DEX-R group (43 min) or Ropivacaine alone (47 min). No adverse-effects were reported in any of the study groups [21]. These two studies show that perineural DEX to LAs improves analgesic effect of UNBs.

4. Transversus abdominis plane (TAP) block: Luan H et al., observed that adding 0.5 mcg/kg of DEX to 60 mg Ropivacaine for TAP block in 60 patients undergoing abdominal hysterectomy decreased the mean Sufentanil consumption in 24 hour after surgery from 63.9 mcg to 51.8 mcg (p<0.0001) and the mean frequency of pressing Patient-Controlled Analgesia (PCA) in 24 hour from 8.3 to 5.4 (p<0.001). There was no difference in VAS scores or PONV between the two groups at 24 hour [36]. Another study in 60 patients undergoing bilateral TAP plus rectus sheath block for emergency abdominal surgery showed that adding 0.5 mcg/kg of DEX to 25 mg of Ropivacaine decreased the 24 hour mean Sufentanil requirement from 41.9 to 32.4 mcg (p<0.05) and 24 hour mean frequency of pressing PCA pump from 6.6 to 1.7 (p=0.0001). The DEX-R group had an increase in the mean time to initial press of PCA button (248.5 min from 157.5 min; p<0.001) and mean duration of sensory block (from 365.7 min to 498.6 min; p<0.001) as compared to Ropivacaine alone [37]. Another study compared 0.3 mcg/kg of DEX with 50 mg of Bupivacaine to Bupivacaine alone for bilateral TAP block for donor hepatectomy (n=50). The same dose of drugs was given every 8 hour for 48 hour on the right side via a surgically introduced catheter. There was a decrease in mean morphine consumption in 72 hour postoperative (4 to 1.5 mg; p=0.03), mean time to bowel motility (from 32 to 25.6 h; p=0.01) and mean time to first successful oral intake (from 32.9 to 25.6 h; p=0.01) in DEX-B group [4]. Many other studies have concluded that adding DEX to LAs increased the time to first rescue analgesia, decreased the overall postoperative opioid use, reduce postoperative pain scores and increase patient satisfaction albeit with increase in adverse events [Table/Fig-3] [4,36-51]. However, there is one study that showed that adding 1 mcg/kg of DEX to 15 mL of 0.33% Ropivacaine for TAP block after inducing anaesthesia for elective gastrectomy (n=98) had no difference in pain scores and total tramadol consumption up to 48 hour after surgery [38].

5. Paravertebral block: Dutta V et al., compared DEX-R to Ropivacaine alone for paravertebral block through continuous catheter infusion (72 h postoperative) before inducing anaesthesia

Author [reference]	Type of surgery	Study groups (n)	Statistically significant results	Statistically significant adverse events
Lin YN et al., [34],	Thyroid surgery	Ropivacaine 112.5 mg alone or R (20) 1 mcg/kg DEX-R or D (20)	1. Mean time to onset of sensory block R>D 2. Mean duration of sensory block D>R	1. Sedation D>R 2. Mean blood pressure and heart rate D<R
Santosh BS et al., [33]	Thyroid surgery	Ropivacaine 100 mg alone or R (30) 0.5 mcg/kg DEX-R or D (30)	1. Duration of post-op analgesia D>R 2. Post-op patient satisfaction score at 24h D>R 3. VAS score at 12h and 24 h R>D	None
Elmaddawy AEW et al., [35]	Thyroid surgery	Bupivacaine 35 mg + 50 mcg Epinephrine or BE (21) 40 mcg DEX-BE or D (21)	1. Time to first request of analgesia D>BE 2. Total opioid consumption BE>D 3. VAS from 6h to 16 h BE<D 4. Intraop fentanyl use BE>D	None

[Table/Fig-2]: Randomised controlled studies reporting the addition of DEX to LA agents for Cervical plexus block [33-35].

Author and Year	Type of study	Type of surgery	Study groups (n)	Statistically significant results	Statistically significant adverse events
Almarakbi WA et al., [47],	Double blind RCT	Elective abdominal hysterectomy	Bupivacaine 50 mg alone or B (25) 0.5 mcg/ kg DEX-B or D (25)	1. Time to first dose of IV morphine D>B 2. Total morphine use in 24 h post-op D<B 3. Total number of PCA boluses D<B 4. VAS up to 8 h post-op D<B	Sedation up to 1 h post-op D>B Nausea D>B
Prabha R et al., [43],	Double blind RCT	Elective Inguinal hernia repair	Ropivacaine 100 mg alone or R (30) 0.5 mcg/ kg DEX-R or D (30)	1. Duration of analgesia D>B 2. Post op analgesic consumption D<B 3. Post op VAS from 2 h to 24 h D<B	None
Abdelaal W et al., [49]	Double blind RCT	Cosmetic abdominoplasty	Levobupivacaine 75 mg alone or LB (23) 100 mcg DEX-LB or D (23) Normal saline or NS (23)	1. Time to first IV meperidine D=LB<NS 2. Total meperidine use in 24 h post-op D<LB<NS 3. Immediate post-op VAS D=LB<NS	No difference between D and LB
Rai P et al., [42]	Double blind RCT	Elective cesarean section	Ropivacaine 50 mg alone or R (50) 0.5 mcg/ kg DEX-R or D (50)	1. Time to first IV tramadol D>R 2. Total Tramadol use in 24 h post-op D<R 3. VAS up to 8 h post-op D<R	None
Bisht S et al., [46]	Double blind RCT	Elective Laparoscopic ovarian cystectomy	Bupivacaine 50 mg alone or B (50) 0.5 mcg/ kg DEX-B or D (50)	1. Time to first IV morphine D>B 2. Total morphine use in 24 h post-op D<B 3. Average VAS in 24 h post-op D<B	None
Luan H et al., [36]	Double blind RCT	Elective Abdominal hysterectomy	Ropivacaine 60 mg alone or R (25) 0.5 mcg/ kg DEX-R or D (25)	1. Total Sufentanil use in 24 h post-op D<R 2. Frequency of PCA presses in 24 h post op D<R 3. VAS up to 24 h post-op D=R	None

Suresh Kumar V et al., [40]	Double blind RCT	Elective Lower abdominal surgery	Bupivacaine 50 mg alone or B (30) 0.5 mcg/ kg DEX-B or D (30)	1. Time to first IV Tramadol D>B 2. Total tramadol use in 12 h post-op D<B 3. Average VAS in 12 h post-op D<B	None
Ramya Parameswari A et al., [41]	Double blind RCT	Elective abdominal hysterectomy	Bupivacaine 50 mg alone or B (35) 0.5 mcg/ kg DEX-B or D (35)	1. Time to first IV Tramadol D>B 2. Total tramadol use in 24 h post-op D<B 3. Average VAS in 24 h post-op D<B	None
Kumar et al., [45]	Double blind RCT	Elective lower abdominal surgery	Ropivacaine 75 mg alone or R (30) 0.5 mcg/ kg DEX-R or D (30)	1. Duration of analgesia D>R 2. Average VAS in 24 h post-op D<R	None
Vyas Madhuri S et al., [39]	Double blind RCT	Elective lower abdominal surgery	0.25% Bupivacaine 0.6 mL/ kg alone or B (30) 0.5 mcg/ kg DEX-B or D (30)	1. Time to first IV tramadol D>B 2. Average VAS in 48 h post-op D<B	Sedation up to 24 h post-op D>B HR up to 6 h post-op D<B BP from 2 h to 6 h post-op D<B PONV D>B
Gani TT et al., [51]	Double blind RCT	Elective lower abdominal surgery	Ropivacaine 60 mg alone or R (50) 1 mcg/ kg DEX-R or D (50)	1. Time to first IV Ketorolac D>R 2. Total Ketorolac use in 24 h post-op D<R 3. Average VAS in 24 h post-op D<R	None
Ding W et al., [38]	Double blind RCT	Elective gastrectomy	15 ml of 0.33% Ropivacaine alone or R (31) 1 mcg/ kg DEX-R or D (30) Normal saline or NS (30)	1. Total tramadol use in 48 h post-op D=R<NS 2. Average VAS at rest and on movement in 24 h post-op D=R<NS 3. Patient rated quality of recovery score D=R>NS	No difference between D and R
Xiao F et al., [50]	Double blind RCT	Elective abdominal hysterectomy	Levobupivacaine 100 mg alone or LB (30) 0.5 mcg/ kg DEX-LB or D (30)	1. Duration of analgesia D>LB 2. Total sufentanil use in 24 h post-op D<LB 3. VAS up to 12 h post-op D<LB 4. Patient satisfaction D>LB	None
Mishra M et al., [44]	Double blind RCT	Elective lower abdominal surgery	Ropivacaine 40 mg alone or R (20) 0.5 mcg/ kg DEX-R or D (20)	Average VAS up to 18 h post-op D<R	None
Xu L et al., [37]	Double blind RCT	Emergency abdominal surgery	Ropivacaine 25 mg alone or R (30) 0.5 mcg/ kg DEX-R or D (30)	1. Duration of sensory block D>R 2. Time to first PCA request of Sufentanil D>R 3. Total sufentanil use in 24 h post-op D<R 4. Frequency of PCA presses in 24 h post-op D<R 5. Average VAS at rest and on movement up to 12 h post-op D<R	MAP and HR after skin incision and 30 min intra-op D<R
Aksu R et al., [48]	Double blind RCT	Elective lower abdominal surgery	Bupivacaine 100 mg alone or B (23) 100 mcg DEX-B or D (23) Normal saline or NS (23)	Total morphine use in 24 h post-op D<B<NS Average VAS up to 23 h post-op D<B<NS Patient satisfaction D>B>NS	None
Aboelela MA et al., [4]	Double blind RCT	Elective donor hepatectomy	Bupivacaine 50 mg alone or B (25) 0.3 mcg/ kg DEX-B or D (25)	First time to IV morphine use D>B Total morphine consumption in 72 h post-op D<B Average pain score in 12 h post-op D<B Time to first bowel movement and oral intake D<B	None

[Table/Fig-3]: Studies reporting the addition of DEX to LA agents for Transversus abdominis plane block [4,36-51].

for thoracotomies (n=30). DEX-R group required a lower mean dose of Propofol for induction of anaesthesia (from 74.33 to 49.33 mg; p=0.002), and had lower mean intraoperative Fentanyl use (from 178.67 to 115.33 mcg; p=0.002), mean end-tidal Isoflurane needed to maintain target entropy at all time points, median postoperative morphine requirement (from 9.6 to 3.6 mg; p<0.001) and mean number of morphine doses to keep VAS<4 (from 3 to 1; p<0.001) as compared to Ropivacaine group [52]. In another study by Xu L et al., that included 60 patients undergoing VATS, adding 1 mcg/ kg of DEX to 75 mg of Ropivacaine improved the postoperative VAS pain score (p<0.05) and patient satisfaction score (using 5 point Likert scale, p<0.001) at 48 hour postoperative but did not affect the total consumption of rescue analgesia [53]. Hassan ME et al., used continuous infusion of Bupivacaine and DEX for paravertebral block before inducing anaesthesia for thoracic surgeries (n=40). They found that addition of DEX reduced the mean intra-op fentanyl requirement (80.75 vs. 186 mcg; p<0.001) and mean morphine consumption in the first 24 hour after surgery (2.95 vs. 9.85 mg; p<0.001). In the same study, addition of DEX also improved postoperative pulmonary function tests (mean of percent predicted) including PEFR (65.0 vs. 44.65; p<0.001), FVC (62.95 vs. 44.4; p<0.001) and FEV1 (65.25 vs. 45.15; p<0.001) [54]. None of these studies showed a difference in adverse effects between the study groups. Mohta M et al., showed that adding 1 mcg/ kg of DEX to 0.5% of 0.3 mL/kg Bupivacaine for paravertebral block before breast surgery (n=45) reduced mean intraoperative fentanyl use (54.6 vs. 58 mcg; p=0.004), postoperative morphine use (1.5 vs. 15.3 mg; p<0.001), PONV (26.7% vs. 73.3%; p<0.05) and mean time to mobilization (23.2 vs. 43.4 h; p<0.05). Patients in DEX-B group also had increased mean time to first analgesic request (1683 vs. 380.5 min; p<0.001) and were discharged sooner (5.2 vs. 5.7 days, p<0.05) [5].

6. Femoral never block (FNB): DEX has been studied as an adjuvant to LAs for FNB in four separate studies [Table/Fig-4] [55-57]. The studies consistently showed a beneficial effect of DEX in FNBs. Hypotension and sedation happened more commonly with DEX in two and one study, respectively [Table/Fig-4].

7. Saphenous/adductor canal: Andersen JH et al., conducted a study on 21 healthy volunteers who underwent bilateral adductor canal block, in one thigh with Ropivacaine (100 mg) and DEX (100 mcg) and in the other thigh with Ropivacaine and placebo. They showed a statistically increase in duration of sensory block to temperature (22 vs. 20h), pinprick (23 vs. 20 h), pain during tonic heat stimulation (22 vs. 20 h) and warmth detection threshold (23 vs. 21 h; p<0.05) but not to heat pain detection threshold (21 vs. 20

Author [reference]	Type of study	Type of surgery	Study groups (n)	Statistically significant results	Statistically significant adverse events
Abdulatif M et al., [20]	Double blind RCT	Arthroscopic anterior cruciate ligament reconstruction	Bupivacaine 125 mg alone or B (15) 25 mcg DEX-B or D1 (15) 50 mcg DEX-B or D2 (15) 75 mcg DEX-B or D3 (15)	Mean 24-hour morphine consumption D3=D2<D1=B Mean time to initial request of analgesia D3>D2>D1>B Mean time to motor block D3=D2<D1=B	Hypotension D3>D2=D1=B
Sharma B et al., [56]	Double blind RCT	Total knee arthroplasty	Ropivacaine 40 mg alone or R (25) 1.5 mcg/ kg DEX-R or D (25) Both followed by Ropivacaine bolus and infusion for pain >4 on NRS scale	Time of first report of pain>4 on NRS scale D>R Mean number of Ropivacaine boluses R>D Mean total Ropivacaine consumption in 24- and 48-hours R>D	Systolic BP up to 4-hours post-op R>D Sedation score up to 4-hours post-op D>R Mean BP up to 8-hours post-op R>D
Li J et al., [57]	Double blind RCT	Total knee arthroplasty	Ropivacaine 100 mg alone or R (30) 1.5 mcg/ kg DEX-R or D (30)	VAS at rest up to 48-hours post-op R>D VAS on movement up to 24-hours post-op R>D Post-op knee circumference R>D Joint fluid concentration of IL-6 and PGE-2 up to 48-hours post-op R>D	None
Packiasabapathy SK et al., [55]	Double blind RCT	Total knee arthroplasty	Bupivacaine 50 mg alone or B (20) 1 mcg/ kg DEX-B or D1 (20) 2 mcg/kg DEX-B or D2 (20)	Mean time to first demand of morphine PCA D2>D1>B Mean morphine consumption in 24 hours post-op D2<B, D2=D1, D1=B Median VAS at rest a. Up to 48 hours post op D2<B b. Up to 24 hours post op D2<D1 c. Up to 8 hours post op D1<B Median VAS on passive motion up to 48 hours post op D2=D1<B	None

[Table/Fig-4]: Studies reporting the addition of DEX to LA agents for Femoral nerve block [55-57].

h; p=0.068) in the DEX-R group as compared to Ropivacaine group. They however, concluded that difference may be statistically but may not be clinically relevant [58]. Mild to moderate sedation occurred in all volunteers in the DEX-R group during the first four hours after the block. One participant in the DEX-R group experienced numbness in an area in the leg receiving DEX.

Goyal R et al., conducted a study in 150 patients undergoing bilateral total knee replacement using 75 mg Ropivacaine alone and with two different concentrations of DEX (0.25 and 0.5 mcg/kg) for adductor canal block. The mean duration of analgesia was higher in the 0.5 mcg/kg DEX-R group as compared to Ropivacaine group (18.4 vs 10.8h, p<0.001) but not between the two groups of DEX. Mean tramadol consumption in 24 hour postoperative decreased progressively from Ropivacaine group to 0.25 mcg/ kg DEX-R group to 0.5 mcg/kg DEX-R group (93.9 vs. 76.4 vs. 43.8 mg; p<0.001). Both DEX-R groups had less pain at rest and on movement during 24-hour postoperative period, and walked more steps on day 1 after surgery as compared to Ropivacaine alone (p<0.05) [6].

8. Sciatic nerve block (SNB): Helal SM et al., studied the addition of 100 mcg of DEX to 20 mg of Bupivacaine for combined femoral and sciatic block in 60 patients undergoing below knee surgery. Mean time to first analgesic request was increased from 462.5 to 807.7 (p <0.01) in the DEX-B group. An increase in sensory and motor block duration by 45% and 40% respectively was also noted in DEX-B group compared to Bupivacaine group. Time to sensory and motor block onset decreased by 20% and duration of analgesia increased by 75% in DEX-B group (p<0.01). Six patients (20%) in the DEX-B group had bradycardia as compared to none in the Bupivacaine group (p=0.02) [59].

Hu X et al., studied 60 patients undergoing varicose saphenous vein resection under a combination of femoral, obturator and sciatic (popliteal approach) nerve block. Authors concluded addition of 50 mcg of DEX to 190 mg Lidocaine and 75 mg of Ropivacaine for PSNB increased the mean duration of sensory and motor block from 758 to 935 minutes and 708 to 917 minutes, respectively (p<0.001). The mean time to onset of motor block for tibial and common peroneal nerves decreased from 14 to 10.5 minutes and 13.6 to 9.9 minutes, respectively (p<0.001). There was a decrease in mean time to onset of sensory block for Sural (3.1 vs. 3.9 min), superficial peroneal (4.9 vs. 8.2 min), and medial (10.9 vs. 13.2 min) and lateral planter nerves (6.5 vs. 11.6 min) (p<0.05) but not for lateral sural cutaneous and profundum peroneal nerves (p>0.05). DEX-LR group had higher quality of surgical anaesthesia (excellent in 16/30 vs 10/30 patients, p<0.05) and better sedation scores (using Ramsey sedation score) at 30 minutes after the block (p<0.05). Patient satisfaction was comparable between the two groups. Side effects were not noticed in any group [60].

9. Obturator nerve block (ONB): Lu X et al., studied the addition of 1 mcg/kg of DEX to Lidocaine with epinephrine (1:200,000) for ONB after transurethral resection of urinary bladder tumor in 60 patients. The goal of the study was to detect the median effective concentration (EC50) of Lidocaine for an effective ONB with and without DEX. DEX-L group had decrease in the EC50 of Lidocaine from 0.57% to 0.29% (p<0.001). There were no side effects like hypotension with DEX-L group. The adductor muscle strength between 2 groups was similar (p>0.05) [61].

10. Posterior tibial nerve block: A cross over study in 14 healthy volunteers by Rancourt MP et al., concluded that adding 1 mcg/ kg DEX to 50 mg of Ropivacaine increased the mean duration of sensory block from 16.2 hour to 21.5 hour (p<0.0001) without any difference in sensory block onset time. However, patients in DEX-R group had lower mean systolic and diastolic BP compared to control up to eight hour after the block (p<0.05). HR levels were comparable throughout the study, except at 60 minutes after block when HR was lower in DEX-R group (p<0.01) [62].

As a conclusion, majority of the studies and all the meta-analyses have demonstrated that addition of DEX to LAs leads to better post-procedure analgesia and reduce the postoperative opiate use [3-6,19-22,25-28,31-33,35-52,54-62].

CONCLUSION

Although studied less commonly, DEX may also have a positive impact on postoperative recovery and discharge, besides having a positive effect on postoperative analgesia. These beneficial effects of DEX have to be weighed against cost and increased risk of adverse events associated with DEX. Current evidence supports the use of DEX in moderate doses improves the efficacy of PNBs without increasing the risk of adverse events. Eventually, the decision to use DEX as an adjuvant for PNBs should be made at the institution or provider level.

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