Review Article

Dexamethasone in anesthesia practice: A narrative review

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Abstract

Dexamethasone is routinely used in anesthesia practice and has been regarded as one of the ideal perioperative agents. It is a synthetic glucocorticoid with potent antiinflammatory action. It reduces postoperative nausea and vomiting, pain, postoperative opioid requirements after general anaesthesia as well as spinal anaesthesia. It has been used via intravenous, epidural and perineural routes. It has been used successfully in fascial blocks. It significantly decreases fatigue, shivering and postoperative sore throat and improves quality of recovery.

Keywords: Anesthesia, dexamethasone, pain, postoperative nausea, vomiting

Dexamethasone is a synthetic glucocorticoid with very little mineralocorticoid action. It is a potent anti-inflammatory agent that has 30–40 times the potency of hydrocortisone and is up to 16 times as potent as prednisolone. Its duration of action may be higher, though its biological half-life is about three hours. In comparison to other glucocorticoids, protein binding of dexamethasone is very less. It is mainly metabolized by liver. Its mechanism of action is complex and involves binding of the steroid ring to the receptor effector site, resulting in gene transcription and thereby causing a decreased release of mediators of inflammation like bradykinin, interleukin (IL)-1, IL-2, and IL-6 and decreased production of prostaglandins.[1]

It is routinely used in anesthesia practice and has been regarded as one of the ideal perioperative agents. Its beneficial effects are numerous. It reduces postoperative nausea and vomiting (PONV), pain, postoperative opioid requirements after general anesthesia and spinal anesthesia, as well as decreases rebound pain after peripheral nerve block. Furthermore, it also decreases postoperative fatigue, sleep disturbance, and improves quality of recovery.[2]

Dexamethasone in postoperative nausea and vomiting

PONV adversely affects postoperative recovery and satisfaction of patients and hence is a major problematic issue.[3] The 2013 practice guidelines of the American Society of Anesthesiologists for post-anesthetic care concluded that dexamethasone was advantageous in the prevention of postoperative vomiting and thereby reduced the risk of rescue antiemetics.[4]

The dexamethasone reduces emesis after major gastrointestinal surgery (DREAMS) trial was a large multicenter, randomized trial that investigated whether dexamethasone given before surgery decreased postoperative vomiting in patients scheduled for elective gastrointestinal surgery. One thousand three hundred fifty participants of the age 18 years or older scheduled for elective open or laparoscopic bowel surgery for malignant

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or benign pathology under general anesthesia were included in this trial. Preoperatively during induction of anesthesia, 8 mg intravenous dexamethasone was given and patients were observed for vomiting for 24 hours postoperatively. The authors observed that 172 patients (25.5%) experienced vomiting in the dexamethasone group compared to 223 patients (33%) in the control group ($P = 0.003$). Postoperative antiemetic was administered on request to 265 participants (39.3%) in the dexamethasone group compared to 351 participants (51.9%) in the control group ($P < 0.001$). Participants were examined 30 days postoperatively to investigate incidence of infection at the site of the surgery: no increase was observed.[5]

The postoperative administration of dexamethasone and infection (PADDI) trial is the most up-to-date and comprehensive trial that endorsed dexamethasone's efficiency as an antiemetic and also supported its safety. This trial included 8,725 participants who were scheduled for non-cardiac surgery of at least two hours duration with a skin incision length >5 cm. Eight milligrams of dexamethasone was given intravenously after inducing anesthesia and before incision. The trial concluded that dexamethasone given as a single dose of 8 mg intravenously led to highly significant decrease in PONV. Postoperative nausea and vomiting was observed in 42.2% of patients in the study group, whereas it was observed in 53.9% of patients in the control group (risk ratio = 0.78; 95% CI [0.75, 0.82]). Surgical site infection occurred in 354 patients (8.1%) in the dexamethasone group in comparison to 394 patients (9.1%) in the control group ($P < 0.001$).[6]

Weibel *et al*.,[7] in their Cochrane systemic review and meta-analysis, evaluated efficacy and safety of dexamethasone. They included 585 randomized trials that enrolled 97,516 participants and investigated 44 drugs as single and 51 drugs as combinations in which dexamethasone was directly compared against comparators in up to 120 of these trials intraoperatively. Dexamethasone, when used intraoperatively, halved the risk of postoperative vomiting (risk ratio = 0.51; 95% CI [0.44 to 0.57]). Overall, dexamethasone was observed to be significantly efficacious and safe.

Role in Postoperative Pain

The factors responsible for postoperative pain are direct injury to tissue, inflammation, or nerve injury.[8] Out of these, the major contributory factor is acute inflammation caused due to tissue injury. Dexamethasone results in pain relief by inhibiting peripheral phospholipase and hence decreasing cyclooxygenase and lipoxygenase.[9] As soon as surgical incision is given, various responses such as inflammatory, metabolic, hormonic, and immune responses become activated. These responses may be decreased by dexamethasone due to its anti-inflammatory and immunosuppressive effects: this proves the role of dexamethasone in pain relief.

Dose and timing of dexamethasone administration

For postoperative pain relief, it is very essential to administer optimal dose. Mohtadi *et al*.[9] conducted a study in patients scheduled for laparoscopic cholecystectomy. These authors administered dexamethasone in a dose of 0.1 mg/kg after inducing anesthesia and observed its effects on postoperative pain relief. Pain intensity in dexamethasone group was significantly less after 2, 6, and 12 hours of surgery ($P < 0.01$). Additionally, meperidine usage was significantly less in the dexamethasone group ($P < 0.05$). However, no significant difference was reported in pain intensity at 24 hours, postoperatively ($P > 0.05$). In a study by Joung *et al*.,[10] a single intravenous administration of dexamethasone in a dose of 0.1 mg/kg during preoperative period was not found to reduce opioid consumption and post-thoracotomy pain. In a meta-analysis of 2,751 patients, three doses of dexamethasone were evaluated and compared by Oliveira *et al*.[11] Low dose was <0.1 mg/kg, intermediate dose was 0.1–0.2 mg/kg, and high dose was >0.2 mg/kg. The authors observed that low dose dexamethasone did not have opioid sparing effect. Intermediate dose decreased early and late pain at rest and at movement, as well as had opioid-sparing effects. High-dose dexamethasone resulted in opioid-sparing effects and decreased postoperative pain, but it was not observed to be beneficial when compared with the intermediate dose. The authors concluded that intermediate dose dexamethasone was safe and effective for postoperative pain relief. Furthermore, dexamethasone in a dose of 8 mg was observed to be sufficient in various studies.[12,13]

In addition to dose, the time of administration of dexamethasone is very important. The onset of dexamethasone is 1–2 hours which is required for its diffusion across the cell membrane, resulting in alteration of gene transcription. Administration of dexamethasone 60 minutes or more prior to incision may be significant to decrease pain and inflammation.[14] Early administration of dexamethasone resulted in better postoperative pain relief and also decreased demand for analgesic in different studies.[15,16] Drug, if administered, just before the incision does not suppress inflammatory mediators.

For postoperative pain relief, dexamethasone has been used via various routes: intravenous, epidural, and perineural.

Dexamethasone via intravenous route

Dexamethasone via the intravenous route has been used along with general anesthesia, spinal anesthesia, and peripheral nerve blockade.

A study was conducted by Samona *et al.*[13] to observe the role of dexamethasone in a dose of 8 mg for postoperative pain relief and requirement of narcotic. This study included 102 patients scheduled for total knee arthroplasty under general anesthesia and spinal anesthesia. Pain score at 24 hours was observed to be 4.57 in the dexamethasone group and 6.07 in the control group ($P = 0.003$). Also, narcotic consumption was observed to be less in the dexamethasone group (37.1 mg vs. 73.1 mg; $P = 0.0.020$) . Fukami *et al.*,[17] in their study on patients undergoing laparoscopic cholecystectomy, concluded that dexamethasone when administered at 8 mg intravenously significantly decreased postoperative pain.

Shalu *et al.*[12] conducted a study to observe the effects of 8 mg intravenous dexamethasone on subarachnoid block in participants scheduled for cesarean section. They concluded that administration of dexamethasone led to prolongation of the duration of sensory block (162.5 min vs. 106.16 min) and time of rescue analgesia (8.67 h vs. 4.4 h; $P < 0.001$) without prolonging the motor block duration. Different doses of dexamethasone (8 mg and 16 mg) were compared by Jain *et al.*[15] in patients who underwent infraumbilical surgery under spinal anesthesia. They observed that 16 mg dexamethasone reduced postoperative pain on motion at 24 and 36 hours. However regarding additional demand of analgesic, the authors observed no significant difference.

In addition to its role in systemic analgesia, dexamethasone intravenously has also been found to be beneficial in increasing the duration of peripheral nerve blockade. Dhanger *et al.*[18] used 2 mg dexamethasone, administered intravenously, in a study on participants scheduled for surgery of the upper limb under supraclavicular block and observed that dexamethasone significantly prolonged the duration of analgesia (11.88 ± 1.31 h vs. 6.47 ± 0.93 h; $P < 0.05$). Chalifoux *et al.*[19] compared different doses of intravenous dexamethasone (4 mg and 10 mg) and concluded that 4mg dexamethasone resulted in significant prolongation of duration of interscalene block compared to the placebo group. However, no difference was observed in the duration of analgesia in 4 mg and 8 mg doses.

Dexamethasone via epidural route

The mechanism of action via epidural route may be due to direct membrane stabilizing effect on nerves or direct action on spinal cord by means of transcription factors like nuclear factor kappa B (NF-KB). Hong *et al.*[20] evaluated different doses of epidural dexamethasone and observed that 10 mg dose was more effective than lower dose in patients undergoing gastrectomy. A requirement of fentanyl was also found to be significantly less in patients receiving dexamethasone without any complications.

Razivizadeh affirmed that adding 8 mg of dexamethasone to bupivacaine for epidural anesthesia in participants scheduled for herniorraphy resulted in significant prolongation of duration of postoperative analgesia. Duration of anesthesia was observed to be 692.55 ± 245.88 min in the dexamethasone group compared to 286.59 ± 84.2 min in the control group ($P < 0.001$).[21] There are certain studies regarding comparison of intravenous and epidural routes. Kalappa *et al.*[22] compared the effect of dexamethasone via caudal route with dexamethasone via intravenous route in patients undergoing lumbosacral spine surgeries and observed no statistically significant difference between the two routes. A dose of 8 mg dexamethasone was used via both the routes.

Dexamethasone via perineural route

Perineural 0.1 mg/kg dexamethasone was found to significantly prolong the duration of analgesia in pediatric patients undergoing upper limb surgery in a study by Ribeiro *et al.*[23] When given perineurally, it resulted in vasoconstriction and hence slowed the absorption of local anesthetic agent, thereby increasing its duration of action. Duration of analgesia in patients receiving dexamethasone was observed to be 27.1 ± 13.4 h and was significantly higher in comparison to the control group, in which it was 13.9 ± 11.3 h ($P < 0.05$). Zhao *et al.*,[24] in their study, observed that perineural dexamethasone prolonged the analgesic duration only when epinephrine was co-administered.

Optimal dose is of great significance; thus, to know the optimal dose of dexamethasone via perineural route, a systematic review and meta-analysis was done by Kirkham *et al.*[25] in patients scheduled for upper limb surgery under brachial plexus blockade. This analysis, which included 33 controlled trials, concluded that perineural dexamethasone of 4 mg represented a ceiling dose. Furthermore, prolongation of 6 and 8 hours was observed in combination with short/intermediate or long-acting local anesthetics, respectively. However, perineural dexamethasone remains an off-label route of administration.

Perineural and systemic dexamethasone were compared in terms of analgesic efficacy and side effects in a systematic review and meta-analysis for peripheral nerve blockade. This analysis, which included 11 controlled trials with 914 patients, concluded that perineural dexamethasone resulted in prolonged duration of analgesia when compared to systemic analgesia by a mean difference of three hours (95% CI [1.4, 4.5]; $P = 0.0001$). Furthermore, when analysis of subgroup was done, duration of analgesia was observed to have increased by 21% using bupivacaine (mean difference = 4.0 h; 95% CI [2.8, 5.2]; $P < 0.00001$) and 12% with ropivacaine (mean difference = 2.0 h; 95% CI [−0.5, 4.5]; $P = 0.11$).[26]

A randomized control trial demonstrated the effect of perineural dexamethasone on rebound pain. The incidence of rebound pain was found to be significantly less in patients receiving dexamethasone (7 [11.1%] of 63 patients) compared to the placebo group (28 [48.8%] of 60 patients; risk ratio = 0.238; 95% CI [0.113, 0.504]; $P = 0.001$]. Rebound pain was defined as a transition from well-controlled pain with a numerical rating scale pain score ≤3 to severe pain ≥7 within 24 hours of block.[27]

Dexamethasone in fascial block

Dexamethasone, when used in fascial blocks in combination with ropivacaine, has been observed to prolong the duration of postoperative pain relief significantly. In a study by Gupta *et al.*,[28] the authors used 4 mg dexamethasone with 0.375% ropivacaine on each side for transversus abdominis plane block. Time to first rescue analgesia was found to be 19.04 ± 4.13 h in the dexamethasone group in comparison to the control group, in which it was found to be 11.62 ± 3.80 h ($P < 0.001$). Postoperative tramadol requirement was also observed to be significantly high in the control group ($P < 0.001$). Dexamethasone as an adjuvant to ropivacaine in transversus abdominis plane block has also been found to prolong analgesia and decrease analgesic requirements in patients undergoing total abdominal hysterectomy. Ropivacaine dexamethasone resulted in lower postoperative visual analog scale (VAS) pain scores at 4, 6, and 12 hours in comparison to ropivacaine alone ($P < 0.05$). Longer duration of analgesia (13.2 ± 7.6 vs. 7.1 ± 4.6 h, $P < 0.05$) with decreased demand of analgesic in the first 24 hours (50.2 ± 34 vs. 94 ± 35 mg, $P < 0.001$) were observed in patients receiving ropivacaine dexamethasone as compared to ropivacaine alone.[29]

In a study by Acharya *et al.*,[30] effects of two different doses of dexamethasone (4 mg vs. 8 mg) were compared as adjuvant to levobupivacaine in fascia-iliaca block. It was observed by the authors that 8 mg dexamethasone resulted in longer duration of analgesia (17.02 ± 0.45 h) than 4 mg dexamethasone (14.29 ± 0.45 h) with a P value of 0.000. Also, demand of postoperative analgesic was observed to be significantly higher in the 4 mg group as compared to the 8 mg group ($P = 0.034$). The authors concluded that 8 mg dose of dexamethasone was more efficacious as compared to 4 mg.

Role of Dexamethasone on Neuromuscular Block

A randomized control study observed decrease in duration of rocuronium-induced neuromuscular block when dexamethasone was used. This study included three groups, and dexamethasone was administered in a dose of 8 mg intravenously. In group A, dexamethasone was administered 2–3 h prior to surgery and in group B during induction of anesthesia, and group C served as control group in which dexamethasone was administered after recovery of neuromuscular block. The duration of neuromuscular block was observed to be significantly less in group A (15.8 ± 4.5 min vs. 18.7 ± 5.8 min in the control group, $P = 0.031$). When recovery index was compared, it was found to be significantly less in group A (6.8 ± 1.8 min) as compared to group B (8.1 ± 2.6 min; $P = 0.018$). Furthermore, the recovery to a train of four ratio of 0.9 was shorter in group A (30.4 ± 6.9 min) as compared to group B (36.3 ± 10.7 min, $P = 0.031$). The authors concluded that dexamethasone attenuated rocuronium-induced block by 15%–20% when administered 2–3 h prior to surgery. However, its administration during induction of anesthesia had no influence on neuromuscular block.[31] Similar results have been observed regarding cis-atracurium-induced block.[32]

Role of Dexamethasone in Shivering

Postoperative shivering can influence patient care significantly and emphasis should be given to its prevention and treatment. Shivering can cause sympathetic stimulation, increased oxygen consumption, or increased production of carbon dioxide. Shivering is reduced by dexamethasone as it decreases the gradient between skin and body core temperature. Dexamethasone was compared with pethidine regarding shivering in a randomized double-blind study. The study concluded that dexamethasone was more effective in preventing postoperative shivering as compared to pethidine. Incidence of shivering was significantly less in the dexamethasone group as compared to the control group (10% vs 37.5%; $P = 0.001$).[33] However, no difference was observed in the incidence of shivering between intrathecal dexamethasone and intrathecal pethidine in patients undergoing transurethral prostatectomy under spinal anesthesia.[34]

Role of Dexamethasone in Quality of Recovery

A study conducted by Oliveira *et al.*[35] demonstrated a dose response effect of dexamethasone on quality of recovery after laparoscopic gynecological surgery using the quality of recovery 40 questionnaire (QOR-40). In this study, before induction of general anesthesia, dexamethasone was given at a dose of 0.05 mg/kg or 0.1 mg/kg. The primary objective was global QOR-40 at 24 hours. Global median (IQR) QOR-40 after saline was 171 (160–182), after 0.05 mg/kg dexamethasone was 179 (175–185), and after 0.1 mg/kg it was 193 (192–195). QOR-40 was higher after dexamethasone

as compared to the placebo. Furthermore, dexamethasone at a dose of 0.1 mg/kg was found to be more effective in quality of recovery as compared to 0.05 mg/kg dexamethasone.

Role of Dexamethasone in Postoperative Sore Throat

Postoperative sore throat is a common problem after general anesthesia which is quite distressing for the patient. Dexamethasone is effective in reducing the incidence of postoperative sore throat, whether administered intravenously, topically or via ebulization. Topical dexamethasone has been found to be as effective as intravenous dexamethasone; however, nebulization has been found to be the most effective technique.[36]

Concerns Over the Use of Dexamethasone

Concerns over the use of dexamethasone in anesthetic practice are the increased incidence of infection, poor wound healing, and hyperglycemia. There is no evidence to suggest that dexamethasone in a single dose increases risk of infection and delays wound healing. Also, there is no evidence to suggest hyperglycemia after a single dose of dexamethasone. The PADDI trial is the most up-to-date trial supporting the safety of dexamethasone. Infection at the surgical site was observed in 354 patients (8.1%) who received dexamethasone and in 394 patients (9.1%) in the control group ($P < 0.001$).[6]

Conclusion

Dexamethasone plays a significant and vital role in anesthesia practice. Considering the numerous benefits of dexamethasone, there is nothing against its perioperative use in anesthesia practice. Dexamethasone in a single dose via intravenous route has been found to be safe and useful in the treatment of postoperative nausea and vomiting. It has good analgesic action, both intravenously and epidurally/perineurally. Furthermore, it has been shown to decrease postoperative analgesic requirement in various studies. The controversial role of dexamethasone in causing postoperative infection at the surgical site has not been reported. Overall, side effects of dexamethasone are rare, and its advantages outweigh the risks. Surgical site infection would not be increased by a single dose. Thus, it can be said that dexamethasone in anesthesia practice is an all-purpose substitute when used judiciously as a single dose and there is no need for caution.

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Conflicts of interest
There are no conflicts of interest.

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