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Review Article

# EFFECT OF DIFFERENT DOSES DEXMEDETOMIDINE ON THE RECOVERY PERIOD IN TOTAL INTRAVENOUS ANESTHESIA GUIDED BY ENTROPY INDEX: SYSTEMATIC REVIEW

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## ABSTRACT

**Abstract Background:** In this systematic review our main objective is to determine the different doses of dexmedetomidine and its effect on the recovery of total intravenous anesthesia.

**Methods:**

**Data sources:** The data for this systematic review was collected from three databases namely PubMed, Science Direct, and Scopus were used to recoup papers examining the dexmedetomidine, total intravenous anesthesia, and related research progress published from 2011 to 2020. All the included references were manually checked and patients of age up to 60 years were part of the study**.**

**Inclusion criteria:** The studies included were original publications in English, meta-analysis, cross- sectional studies, and cohort/case-control studies. The main study interest was the use of different doses of dexmedetomidine and its effect on the recovery time during total intravenous anesthesia in patients undergoing frequently performed laparoscopic surgical interventions. The keywords used to find the relevant literature were anesthesia, intravenous anesthesia, total intravenous anesthesia, dexmedetomidine, and different doses of dexmedetomidine childhood. All included studies were explained through outcomes and data.

**Results:** An overview of selection criteria is given in figture.1. Initially, 851 papers were collected by searching with help of different websites using keywords, and 788 papers were rejected due to irrelevant titles, abstracts, disparity in age groups, and inappropriate estimates. 63 papers were found with relevant abstracts and were further studied, of which 45 papers were further rejected. Finally, 18 papers met the exact selection criteria. The selected studies consist on six clinical studies, four randomized control trial, three prospective studies, one control

trial, one cohort study, one efficacy, and two studies reflects the minor adverse effects of dexmedetomidine. All the studies result are elucidated in Table 1 and Table 2

**Conclusion:** We conclude that the administration of intravenous dexmedetomidine acts in conjunction with the other anesthetic agents. This synergic effect significantly plays a role in the recovery period as well as prolong the duration in any case either spinal anesthesia or others.

**Keywords:** dexmedetomidine (DEX), total intravenous anesthesia (TIVA), intravenous aesthesia

## INTRODUCTION

Dexmedetomidine is a strongly recommended intravenous anesthetics α2 adreno-receptor agonist that is used for analgesic effects as well as anesthetic sparing effects.1 As it affects the locus ceruleus portion which is involved to control sleep and respiration, its sedative effect lowers respiratory depression.[2] Dexmedetomidine is mostly administered via intravenous route as a single bolus dose. However, in case of continuous infusion a loading dose might increase the risk of hypertension and bradycardia.[3] Several studies have reported the effect of single bolus administration of intravenous dexmedetomidine during spinal anesthesia with different dose ranges from 0.25 to 1 μg/kg. Different doses range from 0.5 to 1.0μg/kg of signal doses intravenous dexmedetomidine could cause duration divergent of spinal anesthesia.[4] Generally reported studies show that intravenous dexmedetomidine can increase the length of the sensory blockade and to some extent, enhance the motor blockade duration.[5] Ordinarily, the reported maintenance infusion rate from 0.2 to 0.5 μg/kg/h during the whole surgery and 0.25 to 1 μg/kg used an initial loading dose. Dexmedetomidine is mostly preferred as an intravenous infusion in United State because of short half-life.[9]

Moreover, owning to its sympatholytic effect, heart rate and arterial blood pressure fluctuate due to reduction in epinephrine release.[6] The hypotensive response of dexmedetomidine is controlled by endothelial nitric oxide synthase.[7] A study demonstrated the effect of low concentration (0.5 ng/ml) and high concentration (5 ng/ml) of dexmedetomidine on hemodynamic in healthy participants.[8]

At low concentration, it had biphasic outcomes by decreasing the blood pressure and heart rate. On the other hand, at high concentration increase in blood pressure particularly systemic, pulmonary, and venous were noted.[67-70] Although, a 22% increase in coronary vascular resistance and 27% decrease in myocardial flow produced as a result of low concentration.8 High concentration could not affect the myocardial flow but increase the vascular resistance during the infusion state. Reduction of plasma epinephrine and norepinephrine up to 70% at a lower amount of dexmedetomidine and additional reduction was measured during the high concentration.[45-46]

Generally, entropy is designed to assist the management of general anesthesia patients by properly monitoring the regulation of spontaneous brain and facial muscular activity. For this hypnosis measure, an algorithmic process is produced through electroencephalography (EEG) and frontal electromyography (FEMG).[47] Both processes indicate the depth of anesthesia. Response entropy (RE) shows the first value and has a sensitivity for facial muscle activation. This value gives the indication of patients early awaking in response to

external stimuli. State entropy reflects the second value that is based on EEG and helps to identify the anesthetic agents' effect on the brain.[10]

The high value of entropy with irregularity in signals such as amplitude and wavelength indicate the patient is awake. Constant signals produced over time indicate zero entropy along with the suppression of brain activity. RE values lie between the range 0- 100, 0 shows no brain activity while 100 means fully awaked. SE values range 0 indicate no brain activity and 91 shows fully awake.[11-12] In the case of general anesthesia there is no gold standard method for regulating and monitoring the depth of anesthesia.

Twenty hundred years ago inhalation anesthesia was dominant over intravenous anesthesia. As the world starts turning toward advancement and betterment then people got aware of total intravenous anesthesia.[48-49] Now it is a widely adopted technique of anesthesia. This could be attributed to the introduction of anesthetic agents namely opioids, midazolam, propofol, and dexmedetomidine and increasing knowledge on the aforementioned by research. Gradually, the use of anesthetic agents comes with overwhelming advantages of total intravenous anesthesia (TIVA).[50-51] Therefore, in this systematic review our main focus is the use of dexmedetomidine with different doses as well as we will lighten its recovery effects through the total intravenous anesthesia under the guidance of entropy.

## MATERIALS AND METHODS

### Data sources:

The data for this systematic review was collected from three databases namely PubMed, Science Direct, and Scopus and were used to recoup papers examining the dexmedetomidine, total intravenous anesthesia, and related research progress published from 2011 to 2020. All the included references were manually checked and patients of age up to 60 years were part of the study.

### Inclusion criteria:

The studies included were original publications in English, meta-analysis, cross- sectional studies, and cohort/case-control studies. The main study interest was the use of different doses of dexmedetomidine and its effect on the recovery time during total intravenous anesthesia in patients undergoing frequently performed laparoscopic surgical procedures. The keywords used to find the relevant literature were anesthesia, intravenous anesthesia, total intravenous anesthesia, dexmedetomidine, entropy guide, and different doses of dexmedetomidine. All included studies were explained through outcomes and data.

## RESULTS

An overview of selection criteria is given in figture.1. Initially, 851 papers were collected by searching with help of different websites using keywords, and 788 papers were rejected due to irrelevant titles, abstracts, disparity in age groups, and inappropriate estimates. 63 papers were found with relevant abstract and ere further studied and 45 more papers were rejected. Finally, 18 papers were met the exact selection criteria.

The selected studies consist on six clinical studies, four randomized control trial, three prospective studies, one control trial, one cohort study, one efficacy, and two studies reflects the minor adverse effects of dexmedetomidine. All the studies result are elucidated in Table 1 and Table 2

## Adverse effects:

Two studies reported the adverse effects of dexmedetomidine, one case of bradycardia with OR (95%Cl) value 4.74 (2.39-7.69) had a high dose as compared to the other case. One case of hypotension at dose 0.5cmg/kg (OR-95% Cl), 1.5 (0.65-0.45). In second study (OR-95% Cl), 1.03(0.36-1.73) value was measured for both condition hypotension and bradycardia at dose 0.25cmg/kg. Therefore, DEX at high doses have a greater chance to develop bradycardia condition in patients as compare to low doses (table:2).

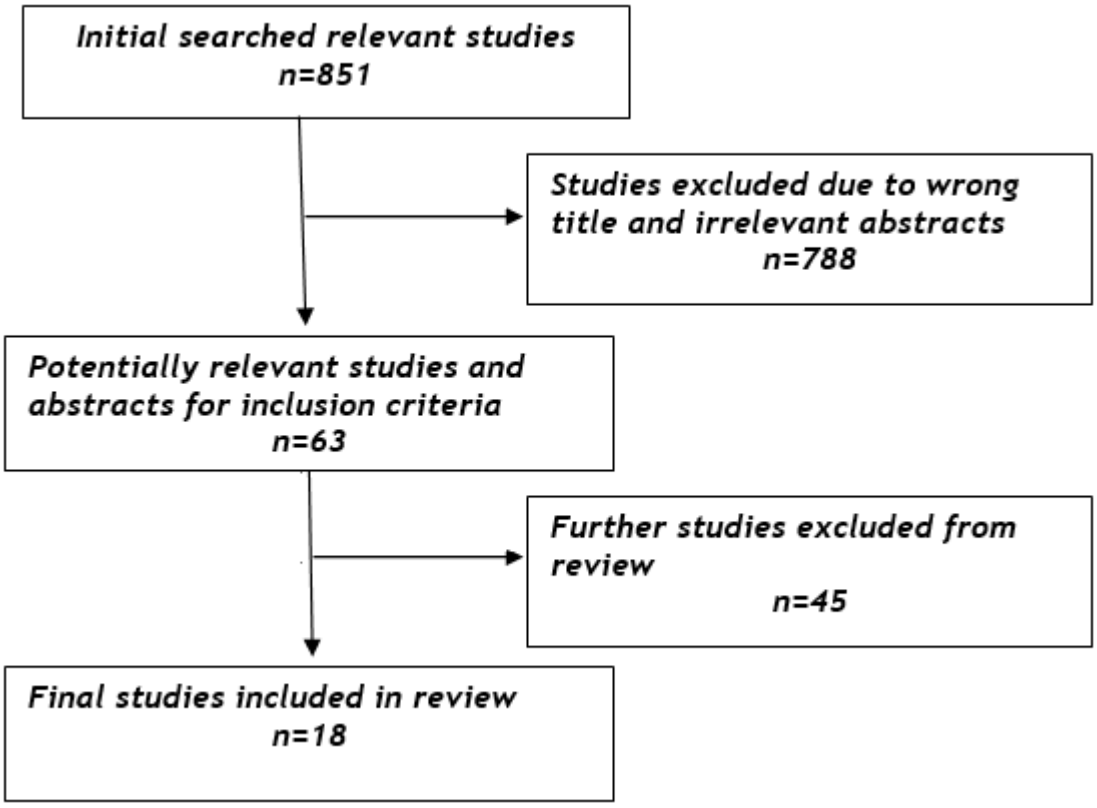


**Figure 1:** The flow diagram of literature selection procedure

| No. | Authors | Study | Dose | Finding |
|---|---|---|---|---|
| 1 | Patel et al., 2012[13] | Clinical study | Loading dose 1μg/kg 10 min before induction | Substantially decrease the stress response at incubation, lesser increase the heart rate 10%, systolic pressure 6% and diastolic 7%. For the post-extubation dexmedetomidine |
| 2 | Rashmi et al., 2016[14] | Clinical study | 0.61μg/kg | Significant results of intravenous dexmedetomidine for laryngoscopy and endotracheal incubation was received in patients of thyroid surgeries |
| 3 | Chaitanya et al., 2014[15] | A prospective study | 1μg/kg | Dexmedetomidine causes the reduction of heart rate and arterial pressure for a short period |
| 4 | Park et al., 2016[16] | A clinical study | 0.3μg/kg/h | Significantly lower mean arterial pressure was noticed for dexmedetomidine. Its low dose of 0.3μg/kg/h decrease the use of propofol and remifentanil for laparoscopic cholecystectomy without the delay in recovery. |
| 5 | Kang et al., 2018[17] | A single center prospective, Double-Blind, Randomized Controlled Trial | 2.0μg/kg | Intravenous (IV) dexmedetomidine at this dose was helpful to enhance the duration of analgesia after single-shot interscalene brachial plexus, without increasing the motor blockade and reduction of opioid use in 24h during arthroscopic shoulder surgery. |
| 6 | Efune et al., 2020[18] | A retrospective cohort study | 0.9μg/kg/h 0.3μg/kg/h | Dexmedetomidine effective doses in children of 2 years as the best option of total intravenous anesthesia. |

| | | | | |
|---|---|---|---|---|
| 7 | Harsoor et al., 2013[19] | A randomized, double-blind, prospective study | 0.5μg/kg over 10 min | IV administration of dexmedetomidine for subarachnoid blocks the duration of sensory and motor with adequate sedation. |
| 8 | Dinesh et al., 2014[20] | A randomized study design | 1μg/kg over 10 min maintain 0.5 mcμg/kg/h | IV dexmedetomidine substantially improves the duration of the motor sensory block during spinal anesthesia. It also had good intraoperative sedation and postoperative analgesia. |
| 9 | Kumari et al., 2017[21] | An efficacy study | 1μg/kg over 10 min maintain 0.6μg/kg/h | Intraoperative sedation score of IV dexmedetomidine (DEX) was higher (mean 3.4±0.6) P<0.05 than the control group. |
| 10 | Rekhi et al., 2017[22] | A control trial | 1μg/kg over 10 min followed by continuous infusion 0.5μg/kg/h | IV DEX significantly (P<0.05) improve the duration of analgesia giving pain relief during the intraoperative and postoperative duration. The recorded sedation score under entry is 3 means fully sleep condition. The recorded duration was 208±19.357 minutes. |
| 11 | Kavy et al., 2018[23] | A clinical study | 0.5μg/kg over 10 min before spinal 0.5μg/kg over 60 min | Motor recovery was significantly prolonged in IV DEX anesthesia that is 302.4min in comparison to 233.4 min for other group |
| 12 | Reddy et al., 2014[24] | A randomize study | 0.5μg/kg over 10 min | Intravenous DEX increase the time (243±38.82 min) of postoperative analgesia as compared to clonidine (190.94± 42.37 min) p<0.0001 |
| 13 | Lee et al., 2014[25] | A prospective study | 0.5μg/kg over 10 min 1μg/kg over 10 min | There was no effective difference between the three groups treated with different doses of dexmedetomidine in case of spinal anesthesia. |

| | | | | |
|---|---|---|---|---|
| 14 | Jung et al., 2013[26] | A clinical study | 0.25 µg/kg over 10 min<br>0.5µg/kg over 10 min | The single dose range of 0.25 to 0.5 was administered that prolong the duration of spinal anesthesia without any side effects. |
| 15 | Chen et al., 2014[27] | A clinical study | 5-10µg/kg/h | Total IV dexmedetomidine had impressively utilized to attenuate the airway activity during laparoscopy and bronchoscope that did not affect the patient's respiratory process |
| 16 | Agrawal et al., 2016[71] | A Comparative study | 0.25 mcg/kg over 15 min | Intravenous dexmedetomidine significantly prolong the duration of sedation during orthopedic surgery |

**Table 1:** Characteristics of studies with different doses of dexmedetomidine

| **Authors** | **Adverse effect** | **Dose** | **Odd ratio (OR), (95% Confidence interval)** | **P-value** |
|---|---|---|---|---|
| Gaitan et al., 2020[28] | 4 patients found with hypotension and bradycardia | 0.25cmg/kg | 1.03(0.36-1.73) | 0.16 |
| Al Nobani et al., 2020[29] | 2 patients with hypotension | 0.5cmg/kg | 1.5 (0.65-0.45) | 0.43 |
| | 2 patients with bradycardia | 1cmg/kg | 4.74(2.39-7.69) | <0.001 |

**Table 2:** Two studies with adverse effects of dexmedetomidine

## DISCUSSION

This systematic review aimed to collect the recent literature on the use of different doses of dexmedetomidine and its effect the recovery period of total anesthesia through the guidance of entropy. For the total intravenous anesthesia, the use of dexmedetomidine had a potential association with analgesia and sedation during surgery especially at dose 0.5-1 mcg/kg/h. Its administration time could be 15-20 minutes before diminishing of procedure for the reduction of anxiety during extubation, reduce the event of postoperative shivering and require for analgesics.[30] 10 to 15 minutes before the start of surgery, this anesthetic agent may be used as a single agent with a dose range of 1 to 5 mcg/kg/h followed by 0.25-1 mcg/kg/h.[31-33]

The duration of local anesthesia can be prolonged by using dexmedetomidine through the different routes especially intravenous. long period of the regional block is observed when DEX is use perineurally[54-56] and the longer duration of subarachnoid block was measured when inserted through the intrathecal route.[57-59]

In case of weak or decline of autonomic response to laryngoscopy and intraocular pressure decrease, inhibition of salivary secretion and awake orotracheal intubation (OTI) is indicated. Therefore, use of dexmedetomidine in this situation better improves the hemodynamic response to OTI as compare to an anesthetic agent such as fentanyl.[34,35,36] Because of its anti-anxiety effects it might be given 90 minutes before surgery. However, it also minimized the cardiovascular effects as well as diminished 30 % requirement of thiopental and opioids.[37]

The use of dexmedetomidine in total intravenous anesthesia was also documented in pediatric patients undergoing spine surgery, endoscopy, and airway instrumentation. Although its effectiveness is limited.[38] One study reported successful use of dexmedetomidine in pediatric patients with dysautonomia along with the reduction of anxiety and hypertensive crises after the surgery.[39]

By exploring extensively, we found more studies on total intravenous anesthesia (TIVA). A case study demonstrated the dose of 10 mcg/kg/h of dexmedetomidine use in total intravenous anesthesia with acceptable hypnosis as well as hemodynamic stability.[42] It can be used in case of laser tracheal ablation, and facial tumor resection. To get cardiovascular and ventilator stability during and after the surgery 5 mcg/kg was used in four pediatric patients.[41]

Another attempt of dexmedetomidine under the guidance of entropy index indicates the wake-up time quality and observes the adverse reactions. Their study results had not found any significant period for the awake or duration of anesthesia while surgery and postoperative wake-up time was significantly identified. The use of dexmedetomidine combined with remifentanil, and propofol under the guidance of entropy index to induce the anesthesia can effectively wake the brain functional area during surgery but the highest wake-up measured through dexmedetomidine.[40]

One more research published about propofol and dexmedetomidine use to perform total intravenous anesthesia in replacement of remifentanil in individuals undergoing gynecological laparoscopy. They had not found any significant adverse effect such as imbalance of serum glucose level, no irregularity with heart rate as well as with blood pressure. Although total recovery time was the same in both groups.[43-44] Two studies evaluate the

different doses of DEX to attenuate the stress response especially in patients undergoing laparoscopic surgical procedures. Results of these studies found significant differences in intubation, insufflation along the extubation. Eventually found the effective dose of DEX to reduce the stress level with better maintenance of anesthesia. A comparison study of remifentanil and DEX concluded that the recovery period of DEX for the postoperative condition was more stable than that of propofol and remifentanil.[60] Therefore, DEX is recommended for use in ameliorated TIVA to enhance stable postoperative recovery.[61] During and after the surgery, arterial blood pressure could be easily maintained through the dexmedetomidine with TIVA and the alternate option is with magnesium sulfate.[62] DEX could effectively control the arterial blood pressure and heart rate. It helps by preventing loss of blood and improve the surgery quality.[63-64] A study demonstrated thoracic surgery with TIVA DEX. The final response of epidural administration of dexmedetomidine decreases the induction dose and times while increasing hemodynamic control during intubation and extubation. Epidural DEX had given the effective analgesia response.[65-66]

## CONCLUSION

Finally, after reviewing most data on dexmedetomidine total intravenous anesthesia. We conclude that the administration of intravenous dexmedetomidine is acting in conjunction with the other anesthetic agents. Which significantly play a role in the recovery period as well as prolong the duration in any case either spinal anesthesia or others. But we notice that the majority of studies recommend its lower dose to get more beneficial changes but it depends on the severity of surgery as well. [52-53]

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