Received: 10 September 2018 | Revised: 13 November 2018 | Accepted: 15 November 2018

DOI: 10.1111/pan.13553

SYSTEMATIC REVIEW

WILEY Pediatric Anesthesia

# A systematic review and narrative synthesis on the histological and neurobehavioral long-term effects of dexmedetomidine

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**Funding information**
Departmental sources and ZonMw80-84800-98-42025.

Section Editor: Laszlo Vutskits

## Summary

**Background:** Recent experimental studies suggest that currently used anesthetics have neurotoxic effects on young animals. Clinical studies are increasingly publishing about the effects of anesthesia on the long-term outcome, providing contradictory results. The selective alpha-2 adrenergic receptor agonist dexmedetomidine has been suggested as an alternative nontoxic sedative agent.

**Aims:** The aim of this systematic review was to assess the potential neuroprotective and neurobehavioral effects of dexmedetomidine in young animals and children.

**Methods:** Systematic searches separately for preclinical and clinical studies were performed in Medline Ovid and Embase on February 14, 2018.

**Results:** The initial search found preclinical (n = 661) and clinical (n = 240) studies. A total of 20 preclinical studies were included. None of the clinical studies met the predefined eligibility criteria. Histologic injury by dexmedetomidine was evaluated in 11 studies, and was confirmed in three of these studies (caspase-3 activation or apoptosis). Decrease of injury caused by another anesthetic was evaluated in 16 studies and confirmed in 13 of these. Neurobehavioral tests were performed in seven out of the 20 studies. Of these seven rodent studies, three studies tested the effects of dexmedetomidine alone on neurobehavioral outcome in animals (younger than P21). All three studies found no negative effect of dexmedetomidine on the outcome. In six studies, outcome was evaluated when dexmedetomidine was administered following another anesthetic. Dexmedetomidine was found to lessen the negative effects of the anesthetic.

**Conclusion:** In animals, dexmedetomidine was found not to induce histologic injury and to show a beneficial effect when administered with another anesthetic. No clinical results on the long-term effects in children have been identified yet.

KEYWORDS
anesthesia, animal experimentation, brain/growth & development, child development/drug effects, dexmedetomidine, general, infant, neurotoxicity, newborn, sedation

## 1 | INTRODUCTION

In December 2016, the FDA issued a warning about the use of general anesthetics and sedative drugs in young children (0-3 years of age) and pregnant women in their third trimester.[1] There is conflicting evidence that currently used anesthetics can affect children's brain development.[2–4] Dexmedetomidine, a highly selective alpha-2 adrenoceptor agonist, is a sedative with analgesic sparing properties. Therefore, it has been suggested as an alternative nontoxic sedative drug.[5] It is already clinically widely used as a sedative in adults and increasingly used in pediatric health care for sedation.[6] Due to its sedative, analgesic and anesthetic-sparing properties, dexmedetomidine can be used for anesthesia or procedural sedation. This might be advantageous in reducing the toxicity of anesthesia and minimizing concerns about adverse effects on children's brains. Still little is known, however, about the toxicity and long-term effects (more than 48 hours after anesthesia) of dexmedetomidine in humans, especially in children.[5,7,8]

Therefore, we performed a systematic review to qualitatively summarize the available information from preclinical studies in young animals and clinical studies in children on the effects of dexmedetomidine on neurotoxicity and neurobehavioral outcome.

### What is already known

- Currently used anesthetics are suggested to be neurotoxic. A possible alternative is dexmedetomidine, which is suggested to be a less neurotoxic and even neuroprotective sedative agent, at least in animal models.

### What this article adds

- Administration of dexmedetomidine in anesthetic practice in preclinical studies show mostly no toxic effects and a decrease of injury caused by other anesthetics. The long-term neurobehavioral outcome following dexmedetomidine administration in children needs to be investigated.

## 2 | MATERIALS AND METHODS

We performed two systematic electronic searches in Embase and Medline Ovid, one for preclinical and one for clinical studies (Appendices 1 and 2) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[9]

The last search in these databases was performed on February 14, 2018. Deduplication of the retrieved citations in the two databases was performed in Endnote.[10]

For preclinical studies, a broad search strategy was used, of which most important terms were: dexmedetomidine, animals, neurotoxicity, development, neuroapoptosis (full search strategy see Appendix 1). Inclusion criteria were: (a) preclinical in vivo study (young animals were alive when exposed to general anesthesia), (b) use of dexmedetomidine as general anesthetic, (c) long-term outcome data reported, and (d) original article or abstract. All studies in which animals suffered encompassing cerebral ischemia were excluded since we aimed to translate the conclusions of the preclinical studies to the use of dexmedetomidine in standard anesthetic care. We included only research on the effects on neonatal and young animals and excluded the research on full-grown animals (rats older than P21, sheep older than gestation days 147, and monkeys older than gestation days 165).[11]

In the search strategy for clinical studies, also a broad search was performed. Of which, most important terms were: dexmedetomidine, neurotoxicity, child, development (full search strategy see Appendix 2). For clinical studies, the following inclusion criteria were applied: (a) dexmedetomidine was administered in children, (b) dexmedetomidine was used as a general anesthetic or sedative, (c) long-term outcome data of neurotoxicity, and (d) original article or abstract.

Two investigators (CvH, HE) independently screened the titles and abstracts of the citations. Those not meeting inclusion criteria according to both screeners were excluded, whereas those on which the screeners disagreed were included for full-text analysis. Thereafter, if available, full-text studies were read independently by the same two investigators, after which their full-text selections were compared and merged. We decided to also include abstracts which present all required information relevant for this systematic review because of the limited number of studies and the fast development of the field of interest. Reviewers resolved discrepancies through discussion or, if needed, by adjudication from the third (JdG) and fourth (SH) reviewer. This resulted in the final selection of studies included in this systematic review.

The primary outcome measure for preclinical studies was the effect of dexmedetomidine on neuronal cells: neurotoxicity or lessening of toxicity caused by another anesthetic agent. This could be measured in two ways: either histological analysis of neuronal cells after exposure to dexmedetomidine (alone or with another anesthetic) in vivo or neurobehavioral tests after exposure to dexmedetomidine.

The primary outcome measure for clinical studies was children's long-term neurobehavioral outcome (more than 48 hours after anesthesia) after administration of dexmedetomidine.

The risk of bias for each included study was established with the SYRCLE's risk of bias tool for preclinical studies.[12,13] Data of the preclinical studies were extracted on a data extraction form made by the authors (CvH, HE), including details of study population (number, animal species, age), intervention (drugs, dose, route of delivery, duration of treatment), and outcome (brain region, histological analysis, neurotoxicity, dexmedetomidine decreases toxicity caused by another anesthetic, neurobehavioral changes).

## 3 | RESULTS

The search strategy for preclinical studies identified 661 studies after deduplication.[10] The initial screening of titles and abstracts

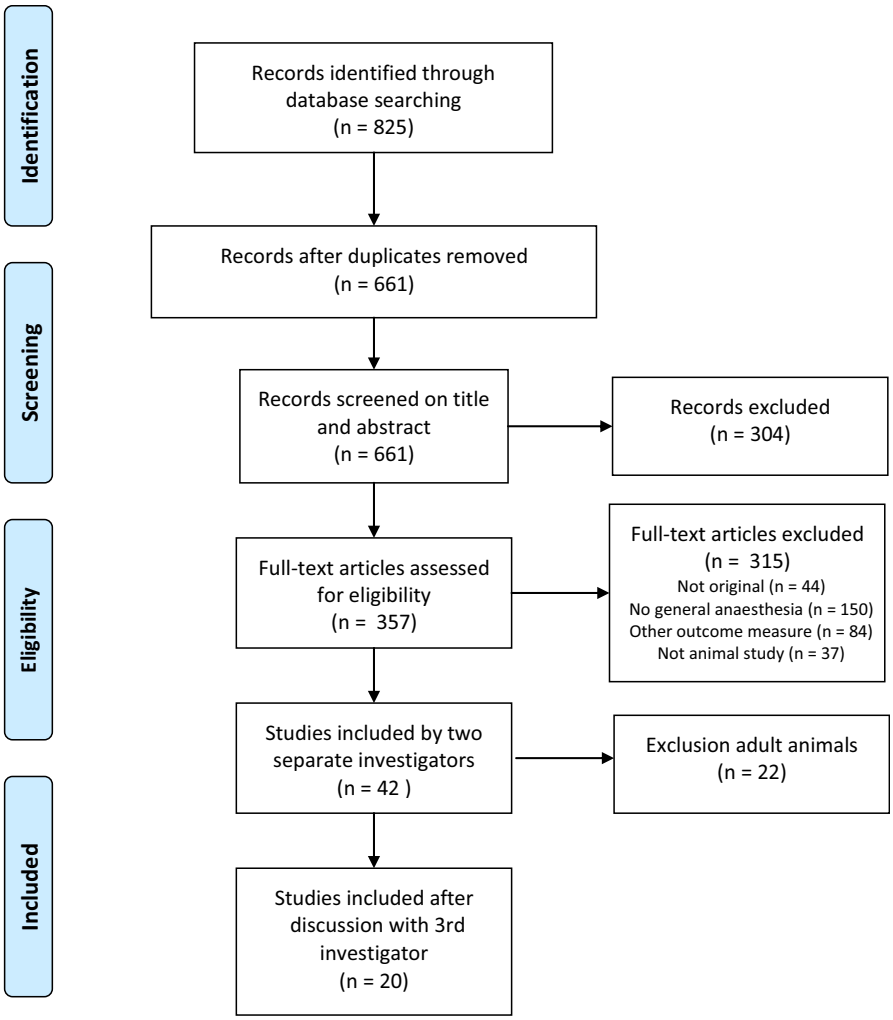


**FIGURE 1** PRISMA Flowchart selection of included preclinical studies. This figure shows an overview of the systematic search results and selection of the studies included for this systematic review. It shows the search found 661 studies, which we reduced to 20 studies included for the preclinical part of this systematic review [Colour figure can be viewed at wileyonlinelibrary.com]

excluded 304 studies; the remaining 357 studies were selected for full-text screening, after which all studies in adult animals were excluded. This resulted in a final selection of 20 preclinical studies included in the systematic review (Figure 1, Table 1).[9]

For the clinical search, 240 studies were identified after deduplication, of which 212 studies were excluded after title and abstract screening. In total, 28 studies were eligible for full-text analysis. This revealed that 25 studies were not original studies and that three studies were case reports. No study fulfilled the inclusion criteria and remained for analysis. This resulted in no included studies (Figure 2).[9]

The risk of bias analysis showed that allocation concealment (timing of randomization) was adequate in all studies and that all but one study were free from selective outcome reporting (Table 1).

Random outcome assessment was reported in none of the 20 studies; blinding for performance (eg, blinding of caregivers and researchers) was reported in seven studies and blinding for detection in 10 studies. No study was completely free from risk of bias (Table 1).

Study characteristics of the 20 included preclinical studies are reported in Table 2. The sample size ranged from 9 to 102 per study and from 2 to 25 animals per group (see Table S1, listing all study characteristics). Studies compared the effect of dexmedetomidine to that of another anesthetic (n = 15), control (saline) (n = 3), or both anesthetic and control (n = 2). In five studies, the anesthetics were administered to the mother during pregnancy and subsequently studied in the newborn animal. In 15 studies, the anesthetics were administered to young animals (P7-P21). Eighteen studies concerned rats, one study pregnant monkeys, and one study pregnant ewes. Dexmedetomidine was mostly injected intraperitoneally, intramuscularly, or subcutaneously. In the monkey[14] and ewe[15] studies, it was injected intravenously and in one other study intracerebroventricularly.[16] It was given as a single or repeated bolus with an interval varying between 1 hour and 7 days. The total dose of dexmedetomidine per animal ranged from 2 to 525 μg/kg. In 17 studies, dexmedetomidine was administered in combination with another anesthetic agent, including ketamine (75 mg/kg intraperitoneal or intravenous infusion at 20 to 50 mg/kg/h for a period of 12 hours),[14,17,18] propofol (intraperitoneal 30 mg/kg/d for a period of 7 days to 100 mg/kg and 1.2 mg/kg/min as continuous infusion for 6 hours),[19–22] and inhalation anesthetic (isoflurane 0.75%-2.0%, sevoflurane 2.5%-4% up to 6 hours).[15,16,22–31]

In total, 18 studies published information about histopathological outcome and seven studies published information about

**TABLE 1** Risk of bias of included studies

| | Sequence generation | Baseline characteristics | Allocation concealment adequately | Random housing | Blinding (performance) | Random outcome assessment | Blinding detection) | Incomplete outcome data | Free from selective outcome reporting |
|---|---|---|---|---|---|---|---|---|---|
| Duan 2014[17] | y | ? | y | y | y | n | ? | y | y |
| Goyagi 2016[23] | n | ? | ? | ? | ? | n | ? | n | ? |
| Han 2013[24] | y | ? | y | ? | ? | n | ? | y | ? |
| Ibrahim 2015[22] | y | ? | y | y | y | n | y | y | y |
| Koo 2014[14] | y | ? | y | ? | ? | n | y | n | y |
| Lee 2017[25] | y | ? | y | y | y | n | y | y | y |
| Li, J 2016[19] | y | ? | y | y | n | n | ? | n | y |
| Li,Y 2014[16] | y | ? | y | ? | ? | n | ? | n | y |
| Liao 2014[26] | n | ? | y | ? | ? | n | ? | n | y |
| Liu 2016[18] | y | ? | y | y | y | n | y | n | y |
| Lv 2017[20] | y | ? | y | y | n | n | ? | n | y |
| Olutoye 2015[15] | n | ? | y | y | n | n | y | n | n |
| Pancaro 2016[32] | y | ? | y | ? | y | n | y | n | y |
| Perez 2017[27] | n | ? | y | y | n | n | y | y | y |
| Sanders 2009[29] | n | ? | y | ? | n | n | y | y | y |
| Sanders 2010[28] | n | ? | y | y | n | n | y | y | y |
| Su 2015[30] | n | ? | y | y | n | n | ? | n | y |
| Tachibana 2011[33] | y | ? | y | y | ? | n | ? | n | y |
| Wang 2016[21] | y | ? | y | y | y | n | y | n | y |
| Zeng 2013[31] | y | ? | y | ? | ? | n | ? | n | y |

N: No; Y: Yes; ?: Not reported; Green: Low risk if bias; Red: High risk of bias.
*Sequence generation*: Was the allocation sequence adequately generated and applied?
*Baseline characteristics allocation*: Were the groups similar at baseline or were they adjusted for confounders in the analysis?
*Concealment adequately*: Was the allocation to the different groups adequately concealed during?
*Random housing*: Were the animals randomly housed during the experiment?
*Blinding (performance)*: Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?
*Random outcome assessment*: Were animals selected at random for outcome assessment?
*Blinding (detection)*: Was the outcome assessor blinded?
*Incomplete outcome data*: Were incomplete outcome data adequately addressed? Has dropouts been reported?
*Free from selective outcome reporting*: Are reports of the study free of selective outcome reporting?

neurobehavioral outcome, of which two studies reported only on neurobehavioral outcome and not on histopathological outcome (Tables 2–4). The effects of dexmedetomidine have been shown using immunohistochemistry, terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL), Western blot, silver staining, and transmission electron microscopy (TEM; Table 3).

## 3.1 | Effect of dexmedetomidine vs control on histopathological outcome

The effects of dexmedetomidine alone on caspase-3 activity were investigated in eight studies (Tables 2 and 3).[14,16,18,19,25,26,29,32] Detection of caspase-3 enables to identify neurons that are undergoing apoptotic degeneration. Less (or similar to control) caspase-3 activity suggests less apoptosis[14,16,19,25,26,29] and more caspase-3 activity suggests more apoptosis after exposure to dexmedetomidine compared to control (Table 3).[18,32] Two studies showed no caspase-3 activity 6 hours after a single or repeated dose of dexmedetomidine varying between 1 and 75 μg/kg.[16,26] In contrast, six other studies did show caspase-3 activity after a total dose of dexmedetomidine ranging from 25 and 250 μg/kg. Of these six studies, four studies found the same amount of activity as in the control group[14,19,25,29] and two studies found more activity than in the control group.[18,32] Additionally, one study investigated synaptic cleft width using electromicroscopy; an increase in width was not shown.[30]

In total, six studies addressed apoptosis in relation to dexmedetomidine alone.[16–18,25,30,32] In two studies, apoptosis increased after a total dose dexmedetomidine ranging from 30 to 250 μg/kg[18,32] and apoptosis had not significantly increased in four studies after a total dexmedetomidine dose ranging from 25 to 100 μg/kg (see Table S1, listing all study characteristics).[16,17,25,28]

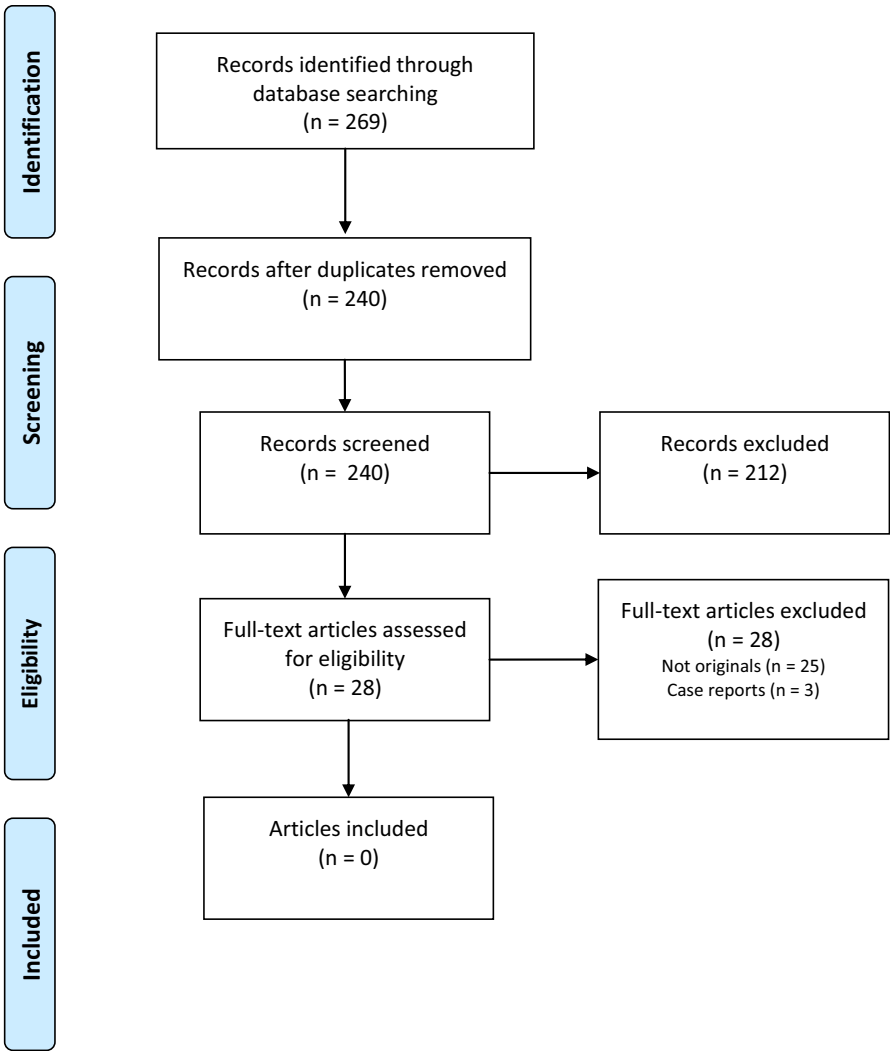


**FIGURE 2** PRISMA Flowchart selection of included clinical studies. This figure shows an overview of the systematic search results and selection of the studies included for this systematic review. It shows the search found 240 studies, which we reduced to 0 studies included for the clinical part of this systematic review [Color figure can be viewed at wileyonlinelibrary.com]

## 3.2 | Effect of dexmedetomidine versus other anesthetic on histopathological outcome

In total, 16 studies reported on dexmedetomidine-induced decrease of injury caused by another anesthetic (Table 2). The other agent was isoflurane in eight studies—0.75% in six studies,[16,24,26,28,29,31] 1.5% in one,[30] and 1.5%-2.0% in one.[15] Total dexmedetomidine dose ranged from 2 to 225 μg/kg. All of these studies show a decrease of isoflurane-induced injury after dexmedetomidine. Two studies studied the effect of dexmedetomidine after sevoflurane administration for 6 hours at 2.5%.[25,27] Of these, one showed a decrease of injury (total dexmedetomidine dose 3-150 μg/kg),[27] whereas the other did not (total dexmedetomidine dose 3-300 μg/kg).[25]

Four studies studied the decrease of injury by dexmedetomidine after injury caused by administration of propofol at a total dose ranging from 4 to 100 mg/kg/d.[19–22] Total dexmedetomidine dose ranged from 3 to 525 μg/kg. Three of the four studies showed a decrease of injury.[19–21] The other study did not show a decrease of injury caused by dexmedetomidine (3 μg/kg) with co-administration of propofol 4 mg/kg or sevoflurane 4.0%.[22]

Two studies studied the decrease of injury by dexmedetomidine after injury caused by ketamine administration.[17,18] One showed a decrease of injury (dexmedetomidine dose 75 μg/kg, ketamine dose 75 mg/kg) caused by dexmedetomidine,[17] whereas the other study (dexmedetomidine dose max. 250 μg/kg, ketamine 20 mg/kg/dose) did not show a decrease of injury.[18]

## 3.3 | Effect of dexmedetomidine on neurobehavioral outcome

In total, seven studies described neurobehavioral testing, all in rodents (Table 2).[17,19,21,23,29,30,33] Three of these studied the effect of dexmedetomidine only (total dose ranged from 3 to 75 μg/kg) on fear conditioning, Morris water maze or synaptic plasticity (Table 4).[29,30,33] None reported any functional impairment caused by dexmedetomidine. Furthermore, in six studies, dexmedetomidine (dose ranging from 3 to 525 μg/kg) decreased the negative effect on neurobehavioral outcome caused by coadministration of ketamine, sevoflurane, propofol, or isoflurane.[17,19,21,23,29,30]

**TABLE 2** Study characteristics

| Article | Study design | Single dose dex (μg/kg) | Total dose dex (μg/kg) | Additional drugs | Histologic injury by dex? | Dex decreases injury caused by other anesthetic | Impaired function after dex | Less impairment after dex (behavior) |
|---|---|---|---|---|---|---|---|---|
| Duan 2014[17] | dex+keta vs dex+con | 25 | 75 | keta: ip 75 mg/kg | No | Yes | — | Yes |
| Goyagi 2016[23] | dex+sevo vs sevo+con | 6.6-12.5-25 | 6.6-12.5-25 | sevo: 3.0% 4 h | — | — | — | Yes |
| Han 2013[24] | dex+iso vs iso+con vs dex | 25 | 75 | iso: 0.75%; sevo: 1.2% 4 h | — | Yes | — | — |
| Ibrahim 2015[22] | dex+sevo vs prop+dex | 3 | 3 | sevo: 4%; prop: iv 4 mg/kg | — | No | — | — |
| Koo 2014[14] | dex vs con | 3.0-30 | 39-390 | keta: 20 mg/kg, 20-50 mg/kg/h 12 h | Yes | — | — | — |
| Lee 2017[25] | dex+sevo vs dex vs sevo | 1-5-25-50-100[a] | 3-15-75-150-300 | sevo: 2.5% 6 h | No[a] | No | — | — |
| Li, J 2016[19] | dex+prop vs dex+iso vs dex | 2.5-5.0-10 | 5-10-20 | prop: iv 8.0 mg/kg+1.2 mg/kg/min | No | Yes | — | Yes |
| Li,Y 2014[16] | dex+iso vs iso+con vs dex | 25-50-75 | 25-50-75 | iso: 0.75% 6 h | No | Yes | — | — |
| Liao 2014[26] | dex+iso vs iso+con | 25-50-75 | 75-150-225 | iso: 0.75% | No | Yes | — | — |
| Liu 2016[18] | dex+keta vs dex vs con | 10-25-50 | 50-125-250 | keta: ip 20 mg/kg per dose | Yes | No | — | — |
| Lv 2017[20] | dex+prop vs con | 25-50-75 | 25-50-75 | prop: ip 100 mg/kg | — | Yes | — | — |
| Olutoye 2015[15] | dex+iso vs iso | 1 | 2 | iso: 1.5%-2.0% 2-3 h+ 6 h | — | Yes | — | — |
| Pancaro 2016[32] | dex vs keta vs con | 30-45 | 30-45 | — | Yes | — | — | — |
| Perez 2017[27] | dex+sevo vs con | 1-5-10-25-50 | 3-15-30-75-150 | sevo: 2.5% 6 h | — | Yes[b] | — | — |
| Sanders 2009[29] | dex+iso vs iso+con | 1-10-25 | 3-30-75 | iso: 0.75% 6 h | No | Yes | No | Yes |
| Sanders 2010[28] | dex+iso vs iso+con | 25-50-75 | 75-150-225 | iso: 0.75% 6 h | No | Yes | — | — |
| Su 2015[30] | dex+iso vs dex+O2 vs con | 10 | 20 | iso: 1.5% 4 h | No | Yes | No | Yes |
| Tachibana 2011[33] | dex vs con | 5-10 | 5-10 | — | — | — | No | — |
| Wang 2016[21] | dex+prop vs con | 75 | 525 | prop: ip 7 days 3x30 mg/kg/d | — | Yes | — | Yes |
| Zeng 2013[31] | dex vs dex+iso vs iso | 25-50-75 | 25-50-75 | iso: 0.75% 6 h | — | Yes | — | — |

dex; dexmedetomidine, keta; ketamine, iso; isoflurane, sevo; sevoflurane, prop; propofol, con; control. WR; Wistar rat, SD; Sprague-Dawley rat, CM; cynomolgus monkey, WE; Western cross ewes, ip; intraperitoneal, sc; subcutaneous, iv; intravenous, im; intramuscular, ICV; intracerebroventricular, cath; catheter, MWM; Morris Water Maze test; h; hours; d; days; w; weeks; m; months; red; toxic effect, green; nontoxic effect/amelioration.

[a]Significant effects from 25 μg/kg and higher

[b]Sevo +high dose of dex leads to increased mortality (dex1:22%; dex5:55%; dex10-25:100%)

**TABLE 3** Histologic tests

| Study | Test +protein | Result dex alone | Result dex +anesthetic |
|---|---|---|---|
| Duan 2014[17] | TUNEL | Dex = control | Less injury |
| Han 2013[24] | TUNEL<br>IHC<br>WB | No dex alone | Less injury |
| Ibrahim 2015[22] | IHC (caspase-3)<br>IMF (caspase-3) | No dex alone | Not less injury |
| Koo 2014[14] | TUNEL<br>TEM (activated caspase-3)<br>SS | Dex = control<br>Dex = control<br>Dex = control | No dex combination |
| Lee 2017[25] | IHC (caspase-3)<br>Microscopy (apoptosis) | Dex = control[a]<br>Dex = control | Not less injury |
| Li 2016[19] | WB (caspase-3)<br>IMF (caspase-3) | Dex = control<br>Dex = control | Less injury |
| Li 2014[16] | TUNEL<br>IHC (caspase-3)<br>WB (caspase-3) | Dex = control<br>Dex no caspase-3 activation<br>Dex = control | Less injury |
| Liao 2014[26] | TUNEL<br>WB (caspase-3) | Dex = control<br>Dex no caspase-3 activation | Less injury |
| Liu 2016[18] | TUNEL (proteinase K)<br>IHC (caspase-3)<br>WB (cleaved caspase-3)<br>IMF (caspase-3) | Dex > control<br>Dex > control<br>Dex > control<br>Dex > control | Not less injury |
| Lv 2017[20] | TUNEL (proteinase K)<br>WB (p-Akt and Akt)<br>IMF (primary antibody)<br>TEM | No dex alone | Less injury |
| Olutoye 2015[15] | IHC (anti-human/mouse caspase-3) | No dex alone | Less injury |
| Pancaro 2016[32] | IHC (rabbit anti-cleaved caspase-3)<br>SS | Dex > control<br>Dex > control | No dex combination |
| Perez 2017[27] | Microscope (rabbit anti-cleaved caspase-3) | No dex alone | Less injury[b] |
| Sanders 2009[29] | IHC (rabbit anti-cleaved caspase-3) | Dex = control | Less injury |
| Sanders 2010[28] | IHC (rabbit anti-cleaved caspase-3) | No apoptosis | Less injury |
| Su 2015[30] | TEM | Dex = control | Less injury |
| Wang 2016[21] | TUNEL<br>WB (caspase-3) | No dex alone | Less injury |
| Zeng 2013[31] | TUNEL<br>WB (?) | No dex alone | Less injury |

TUNEL; Terminal deoxynucleotidyl transferase dUTP nick end labeling, IHC; immunohistochemistry, WB; Western blot, IMF; immunofluorescence, TEM; transmission electron microscopy, SS; silver staining, Dex; dexmedetomidine.
[a]If dex < 25 μg/kg dex = control. If dex > 25 μg/kg dex > control
[b]Only when low-dose dex was administered in combination with another anesthetic

## 4 | DISCUSSION

In a recently published review, dexmedetomidine was proposed as a suitable alternative for currently used, allegedly toxic anesthetics in children, and has been suggested to have a neuroprotective effect when coadministered with these anesthetics.[5] In this systematic review, we analyzed the results of both preclinical and clinical studies to assess whether dexmedetomidine is a suitable alternative for the allegedly neurotoxic anesthetic agents. In preclinical studies, exposure to dexmedetomidine alone had contradictory effects on caspase-3 activity by histologic examination; no differences with controls in six studies (total dexmedetomidine dose ranging from 3 to 300 μg/kg),[14,16,19,25,26,29] more caspase-3 activity in three other studies (total dexmedetomidine dose ranging from 30 to 250 μg/kg).[14,18,32] Coadministration of dexmedetomidine (total dexmedetomidine dose ranging from 3 to 525 μg/kg) decreased the negative histologic effect caused by other anesthetics in 13 studies[15–17,19–21,24,26–31] but the effect was not found in three other studies.[18,22,25] All six studies that report on adverse neurobehavioral outcome showed a decrease of injury when coadministration of dexmedetomidine (dose ranging from 3 to 525 μg/kg) with other anesthetics (isoflurane, sevoflurane, ketamine, or propofol).[17,19,21,23,29,30] To evaluate neuronal injury, most

**TABLE 4** Neurobehavioral tests

| Study | Morris water maze test | Other |
|---|---|---|
| Duan 2014[17] | + | |
| Goyagi 2016[23] | + | |
| Li 2016[19] | | Eight-arm radial maze test |
| Sanders 2009[29] | | Fear conditioning |
| Su 2015[30] | + | |
| Tachibana 2011[33] | | Synaptic plasticity |
| Wang 2016[21] | + | |

Test performed by study is denoted by '+'.

studies focused on testing for apoptosis. Other signs of neuronal injury, such as synaptogenesis and gliogenesis were not used as markers for neuronal injury by most studies, except for one, which studied synaptic width to evaluate neuronal injury.[30]

Furthermore, our systematic search did not yield clinical studies on children's neurobehavioral outcomes after administration of dexmedetomidine as a sedative agent. Excluded were studies that evaluated acute effects after anesthesia (eg, agitation and delirium), since the aim of this study was to evaluate effects on the long term (more than 48 hours after anesthesia) only. Although an increase in publications on dexmedetomidine administration in children for sedation, pain management, and delirium management is noted, studies focusing on long-term effects are not published yet.

The reviewed preclinical studies overall show an advantageous effect of dexmedetomidine regarding neurotoxicity. Histologically, neurons show less apoptosis after exposure to dexmedetomidine compared to exposure to other anesthetics (see results).[14,16,19,25,26,29] Most of the histologic research focuses on a basic element of toxicity: apoptosis (and the connected caspase-3 activity). Apoptosis is programmed cell death, which can be triggered by cell damage. Cell damage can activate caspase-3 as a precursor in the pathway that leads to apoptosis.[34] Apoptosis can be marked histologically with techniques like terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL), silver staining, and Western blot. Using these techniques, a few study results show brain damage induced by dexmedetomidine; caspase-3 activity was increased in animals (Sprague-Dawley rats) after exposure to dexmedetomidine.[14,18,25,32]

Out of the 18 studies that performed histological analysis, 16 addressed decrease of injury caused by another anesthetic agent. Thirteen of these found a decrease of injury, suggestive of a neuroprotective effect of dexmedetomidine. Only one study shows major negative effects of dexmedetomidine coadministered with another anesthetic. The mortality rate among Wistar rats in that study was not affected when either sevoflurane 2.5% or dexmedetomidine (5, 25 or 50 μg/kg) was administered alone, but a significant increase in dose-dependent mortality and neuronal cell apoptosis was seen when a total dose of dexmedetomidine ranging from 3 to 150 μg/kg was co-administered with 2.5% sevoflurane. In the surviving animals, however, coadministration of low dose dexmedetomidine (1 and 5 μg/kg) lead to a significant reduction in sevoflurane-induced apoptosis.[27] Hypothetically, the increased mortality (like suggested by one study that found increased mortality) might be a sevoflurane overdose leading to too deep levels of anesthesia resulting in death.[25]

Neurobehavioral outcome in animals can be tested by learning tasks (radial maze), executive tasks (motor skills), memory (eight-arm radial maze test), and social skills (fear conditioning). Seven studies performed neurobehavioral tests, of which the Morris Water Maze test was used the most.[17,21,23,30] This test is used in rodents for assessing spatial learning and memory. Three of these studies examined whether administration of dexmedetomidine alone causes impaired outcome.[29,30,33] These studies showed that the outcome of the tests is worse after exposure to anesthetics compared to control. Six studies showed that when the rats were subsequently exposed to dexmedetomidine, performance improved, which indicates that dexmedetomidine decreases the negative effects caused by other anesthetics on the neurobehavioral outcome in all tests.[17,19,21,23,29,30]

Furthermore, overall, studies show that dexmedetomidine itself does not have a negative effect on task execution and that it ameliorates the negative effects caused by other toxic anesthetics.

Anesthetics were mostly injected intraperitoneal, because intravenous access is challenging in small animals.[35] The total dexmedetomidine dose administered varied widely between the included studies, from 3 to 525 μg/kg, in contrast to standard doses of sevoflurane (2.5%-4.0%) and isoflurane (0.75%).

The results of the preclinical studies suggest a neuroprotective profile in animals. However, although there is a logical relation between experimental and clinical studies, not all pathophysiological mechanisms can be translated 'from bench to bed'.[36–39] For example, where sevoflurane is nephrotoxic in preclinical studies, this appears not to hold for humans.[40] On the other hand, interventions that are harmful in clinical studies may not be harmful in preclinical studies.[41–43] Preclinical studies usually examine toxicity of interventions, pathology and mechanisms of disease, whereas clinical studies focus on clinical efficacy.[44] Considering these different study objectives, differences in outcome between preclinical and clinical studies are not that unexpected. Still, only clinical studies following sufficient reliable proof from preclinical studies could give an indication of the safety of new drugs/treatments in humans.[45]

Furthermore, although an animal data on the large doses of dexmedetomidine is important and fully within concept of animal research, it may not be extrapolated to humans: in humans, dexmedetomidine is used either as a sedative or as an adjunct to other anesthetics, but never as a "sole anesthetic."

The present systematic review makes clear that the long-term effects of dexmedetomidine in children are not known yet. The milestones of neurobehavioral development vary across species but the developmental progression in general is comparable. In the first weeks of life, critical neurodevelopment occurs; apoptosis, synaptogenesis, gliogenesis, and myelination, regardless of biological differences between species.[46]

There are some considerations regarding this review. All studies in which animals had suffered cerebral ischemia were excluded. Still,

this is a large group in which dexmedetomidine is suggested to have a (neuro)protective effect.[7,47,48] The results of these studies might give more information about the effects of dexmedetomidine on the brain that could help to determine whether dexmedetomidine administration would be applicable and/or beneficial for secondary prevention after ischemic brain injury. Furthermore, studies that did not report dexmedetomidine as a general anesthetic agent were excluded. We aimed to address the effect of dexmedetomidine on the neurons in the brain, and deemed general anesthesia to be the best fit to do so. We reasoned that in other applications of anesthesia (such as local anesthesia and nerve block), the drug would possibly not reach the brain.

Importantly, the quality of the studies included in the present systematic review was intermediate. Not all studies randomly assigned the animals to the groups, which could have led to confounding. Furthermore, methodological descriptions are often poorly reported. Most important issues are the descriptions of dropouts and detailed description of the intervention (dose). Only eight out of 20 studies reported on the mortality of the experiment (see Table S1, listing all study characteristics). When studied animals are replaced after dropout without description, important outcome can be missed.

Lastly, we performed a broad search in two databases without any language limitations or exclusions due to language barriers. Still, we may have missed relevant studies, with the concomitant risk of search bias. Furthermore, non-reporting of study results could have given rise to publication bias (not reporting certain outcomes) and/or author bias (judgment of the authors of the study).[49]

In conclusion, the overall trend of the results shows a substantial variety in species, exposure paradigm, and histological assessment to render conclusive results. A clear conclusion cannot be stated: eight out of 11 studies demonstrated no histological injury by dexmedetomidine when administered by itself and 13 out of 16 studies found beneficial neuroprotective effects of dexmedetomidine coadministrated with other anesthetics.

Dexmedetomidine is currently clinically used, however, as our systematic search shows, studies are lacking about the long-term neurobehavioral effects when administered in children for sedation or anesthesia. A randomized controlled trial to find out what the long-term neurobehavioral effects of dexmedetomidine are in children (compared to currently used neurotoxic anesthetics), with the ultimate aim to find a safe(r) alternative to the currently used neurotoxic anesthetics in children is mandatory. Furthermore, the safety of the combination of dexmedetomidine (especially in high dose) with other anesthetics needs to be monitored meticulously.

## ACKNOWLEDGMENTS

We thank Ko Hagoort of the Erasmus MC-Sophia Children's Hospital, Rotterdam for his editorial assistance and Wichor M. Bramer, Biomedical Information Specialist, Medical Library, Erasmus MC–Erasmus University Medical Centre, Rotterdam for helping to construct the search in Embase and Medline Ovid.

## ETHICAL APPROVAL

Not applicable.

## CONFLICT OF INTEREST

The authors report no conflict of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**How to cite this article:** van Hoorn CE, Hoeks SE, Essink H, Tibboel D, de Graaff JC. A systematic review and narrative synthesis on the histological and neurobehavioral long-term effects of dexmedetomidine. *Pediatr Anesth*. 2019;29:125–136. https://doi.org/10.1111/pan.13553

# APPENDIX 1

## SEARCH PRECLINICAL STUDIES

### Embase

('dexmedetomidine'/exp OR (dexmedetomidine OR cepedex OR dexamedetomidine OR dexdomitor OR dexdor OR mpv-1440 OR mpv1440 OR precedex OR primadex OR sedadex OR sileo):ab,ti) AND ('neurotoxicity'/exp OR 'toxicity and intoxication'/de OR intoxication/de OR 'drug intoxication'/de OR 'neuroprotection'/de OR 'toxicity'/de OR 'brain toxicity'/exp OR 'drug toxicity'/de OR 'behavior change'/exp OR 'behavior disorder'/exp OR 'neuropsychology'/de OR 'memory disorder'/de OR 'cognitive defect'/de OR 'developmental toxicity'/de OR 'nervous system development'/exp OR 'developmental disorder'/de OR cognition/de OR learning/exp OR memory/exp OR 'mental capacity'/exp OR 'mental development'/exp OR 'mental performance'/exp OR 'social cognition'/exp OR 'experimental behavioral test'/exp OR 'neuropsychological test'/exp OR (neurotoxic* OR neuroprotect* OR toxic* OR intoxicat* OR (behav* NEAR/3 (change* OR test OR disorder*)) OR memor* OR neuropsycholog* OR cogniti* OR learning OR neurocogniti* OR ((development*) NEAR/3 (disorder* OR dysfunct* OR function* OR declin* OR defect* OR impair* OR improv*)) OR (maze NEAR/3 test*) OR (('nervous system' OR brain) NEAR/3 (develop*)) OR neuroapoptos* OR adhd OR (attention NEAR/3 (deficit OR hyperactiv*)) OR iq OR intelligence OR autis*):ab,ti) AND ([animals]/lim OR nonhuman/de OR (rat OR rats OR mouse OR mice OR murine OR animal* OR monkey* OR makak* OR primate* OR nonhuman):ab,ti)

### Medline ovid

(Dexmedetomidine/OR (dexmedetomidine OR cepedex OR dexamedetomidine OR dexdomitor OR dexdor OR mpv-1440 OR mpv1440 OR precedex OR primadex OR sedadex OR sileo).ab,ti.) AND (Neurotoxicity Syndromes/OR neuroprotection/OR toxicity.xs. OR Memory Disorders/OR Cognitive Dysfunction/OR nervous system/gd OR Neuropsychology/OR Developmental Disabilities/OR cognition/OR Cognition Disorders/OR learning/OR exp memory/OR Neuropsychological Tests/OR (neurotoxic* OR neuroprotect* OR toxic* OR intoxicat* OR (behav* ADJ3 (change* OR test OR disorder*)) OR memor* OR neuropsycholog* OR cogniti* OR learning OR neurocogniti* OR ((development*) ADJ3 (disorder* OR dysfunct* OR function* OR declin* OR defect* OR impair* OR improv*)) OR (maze ADJ3 test*) OR ((nervous system OR brain) ADJ3 (develop*)) OR neuroapoptos* OR adhd OR (attention ADJ3 (deificit OR hyperactiv*)) OR iq OR intelligence OR autis*).ab,ti.) AND ((exp animals/NOT humans/) OR (rat OR rats OR mouse OR mice OR murine OR animal* OR monkey* OR makak* OR primate* OR nonhuman).ab,ti.)

# APPENDIX 2

## SEARCH CLINICAL STUDIES

### Embase

('dexmedetomidine'/exp OR (dexmedetomidine OR cepedex OR dexamedetomidine OR dexdomitor OR dexdor OR mpv-1440 OR mpv1440 OR precedex OR primadex OR sedadex OR sileo):ab,ti) AND ('neurotoxicity'/exp OR 'toxicity and intoxication'/de OR intoxication/de OR 'drug intoxication'/de OR 'neuroprotection'/de OR 'toxicity'/de OR 'brain toxicity'/exp OR 'drug toxicity'/de OR 'behavior change'/exp OR 'behavior disorder'/exp OR 'neuropsychology'/de OR 'memory disorder'/de OR 'cognitive defect'/de OR 'developmental toxicity'/de OR 'nervous system development'/exp OR 'developmental disorder'/de OR cognition/de OR learning/exp OR memory/exp OR 'mental capacity'/exp OR 'mental development'/exp OR 'mental performance'/exp OR 'social cognition'/exp OR 'experimental behavioral test'/exp OR 'neuropsychological test'/exp OR (neurotoxic* OR neuroprotect* OR toxic* OR intoxicat* OR (behav* NEAR/3 (change* OR test OR disorder*)) OR memor* OR neuropsycholog* OR cogniti* OR learning OR neurocogniti* OR ((development*) NEAR/3 (disorder* OR dysfunct* OR function* OR declin* OR defect* OR impair* OR improv*)) OR (maze NEAR/3 test*) OR (('nervous system' OR brain) NEAR/3 (develop*)) OR neuroapoptos* OR adhd OR (attention NEAR/3 (deficit OR hyperactiv*)) OR iq OR intelligence OR autis*):ab,ti) AND (child/exp OR adolescent/exp OR adolescence/exp OR pediatrics/exp OR childhood/exp OR 'child development'/de OR 'child growth'/de OR 'child health'/de OR 'child health care'/exp OR 'child care'/exp OR 'childhood disease'/exp OR 'pediatric ward'/de OR 'pediatric hospital'/de OR (adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*):ab,ti) AND ('anesthesia'/exp OR 'anesthetic agent'/de OR (anesthe* OR anaesthe*):ab,ti) NOT ([animals]/lim NOT [humans]/lim)

### Medline Ovid

(Dexmedetomidine/OR (dexmedetomidine OR cepedex OR dexamedetomidine OR dexdomitor OR dexdor OR mpv-1440 OR mpv1440 OR precedex OR primadex OR sedadex OR sileo).ab,ti.) AND (Neurotoxicity Syndromes/OR neuroprotection/OR toxicity.xs. OR Memory Disorders/OR Cognitive Dysfunction/OR nervous system/gd OR Neuropsychology/OR Developmental Disabilities/OR cognition/OR Cognition Disorders/OR learning/OR exp memory/OR Neuropsychological Tests/OR (neurotoxic* OR neuroprotect* OR toxic* OR intoxicat* OR (behav* ADJ3 (change* OR test OR disorder*)) OR memor* OR neuropsycholog* OR cogniti* OR learning OR neurocogniti* OR ((development*) ADJ3 (disorder* OR dysfunct* OR function* OR declin* OR defect* OR impair* OR improv*)) OR (maze ADJ3 test*) OR ((nervous system OR brain) ADJ3 (develop*)) OR neuroapoptos* OR adhd OR (attention ADJ3 (deificit OR hyperactiv*)) OR iq OR intelligence OR autis*).ab,ti.) AND (exp Child/OR exp Infant/OR exp Adolescent/OR exp "Child Behavior"/OR exp "Parent Child Relations"/OR exp "Pediatrics"/OR "Child Nutrition Sciences"/OR "Infant nutritional physiological phenomena"/OR exp "Child Welfare"/OR "Child Development"/OR exp "Child Health Services"/OR exp "Child Care"/OR "Child Rearing"/OR exp "Child development Disorders, Pervasive"/

OR "Child Psychiatry"/OR "Child Psychology"/OR "Hospitals, Pediatric"/OR exp "Intensive Care Units, Pediatric"/OR (adolescen* OR infan* OR newborn* OR (new ADJ born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under ADJ1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*).ab,ti.) AND (exp anesthesia/ OR anesthetics/OR (anesthe* OR anaesthe*).ab,ti.) NOT (exp animals/NOT humans/)