The Hierarchy of Evidence

The Hierarchy of evidence is based on summaries from the National Health and Medical Research Council (2009), the Oxford Centre for Evidence-based Medicine Levels of Evidence (2011) and Melynyk and Fineout-Overholt (2011).

I Evidence obtained from a systematic review of all relevant randomised control trials.

II Evidence obtained from at least one well designed randomised control trial.

III Evidence obtained from well-designed controlled trials without randomisation.

IV Evidence obtained from well designed cohort studies, case control studies, interrupted time series with a control group, historically controlled studies, interrupted time series without a control group or with case-series

V Evidence obtained from systematic reviews of descriptive and qualitative studies

VI Evidence obtained from single descriptive and qualitative studies

VII Expert opinion from clinicians, authorities and/or reports of expert committees or based on physiology


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Databases searched:
- CINAHL (Ebsco)
- Medline (Ebsco)
- Pubmed (NLM)
- Nursing (Ovid)
- Emcare (Ovid)

Keywords used: CINAHL Headings “Neonate” and “Pain Management”

Search limits: Year: 2016-2021

Other search comments: __________
<table>
<thead>
<tr>
<th>Reference (include title, author, journal title, year of publication, volume and issue, pages)</th>
<th>Evidence level (I-VII)</th>
<th>Key findings, outcomes or recommendations</th>
</tr>
</thead>
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| Zhu A, Benzon HA, Anderson TA. Evidence for the Efficacy of Systemic Opioid-Sparing Analgesics in Pediatric Surgical Populations: A Systematic Review. Anesthesia And Analgesia. 2017;125(5):1569-87. doi: 10.1213/ANE.0000000000002434. PubMed PMID: 29049110. | I | • Acetaminophen, even a single pre- or intraoperative dose, regardless of the route used, appears to be effective at decreasing postoperative pain and/or opioid consumption after a variety of paediatric surgeries as long as a therapeutic dose is used.  
• Oral clonidine at a dose of 4 μg/kg decreases postoperative pain measures in children after a variety of minor surgeries.  
• Intraoperative dexmedetomidine, especially if at least 0.5 μg/kg is given, decreases postoperative pain measures in paediatric patients after a variety of ambulatory surgeries. |
• Paediatric trials are therefore needed, with a specific focus on newborns and infants, taking into account the major side effects documented in the literature for dexmedetomidine, hypotension and bradycardia, for which continuous cardiac monitoring is needed  
• Interestingly, rodent studies have shown that dexmedetomidine and clonidine may reduce anaesthetic-induced apoptosis, specifically in the hippocampus, and diminish subsequent cognitive decline.  
• Exposure to propofol and midazolam in the neonatal period has been suggested to negatively affect the developing brain in animals and humans. Although studies in humans are scarce, findings from experimental studies suggest that, in particular, hippocampal development and long-term learning memory are affected after exposure to these agents |
| Michel J, Hofbeck M, Peper A-K, Kumpf M, Neunhoeffer F. Evaluation of an updated sedation protocol to reduce benzodiazepines in a pediatric intensive care unit. 2020. p. 1-6. | VI | Sedation protocol involved not starting a midazolam infusion automatically. Increase the morphine and then start clonidine infusion 0.5-2mcg/kg/hr.  
Midazolam used as bolus if required. Less midazolam, slightly more morphine and clonidine. No difference with withdrawal and delirium. |
• Single-bolus doses of dexmedetomidine decreased the proportion of damaged neurons and reduced lesion size in rodent models of PVL. Similar evidence of neuroprotection was found in models of hypoxic-ischemic injury.  
• Preclinical data also suggest an anti-inflammatory role of dexmedetomidine, which has the potential to impact common morbidities in premature neonates, including infection and ventilator induced lung injury leading to bronchopulmonary dysplasia |
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<td>Abiramalatha T, Mathew SK, Mathew BS, Shabeer MP, Arulappan G, Kumar M, et al. Continuous infusion versus intermittent bolus doses of fentanyl for analgesia and sedation in neonates: an open-label randomised controlled trial. Archives Of Disease In Childhood Fetal And Neonatal Edition. 2019;104(4):F433-F9. doi: 10.1136/archdischild-2018-315345. PubMed PMID: 30322973.</td>
<td>II</td>
<td>This RCT with 100 neonates (15 of these below 27 weeks gestation) found that continuous fentanyl was more effective than intermittent boluses of fentanyl and provide a steady concentration in blood serum, despite beliefs that the half-life of fentanyl in neonates is longer due to delayed hepatic clearance because of the immature liver and liver enzymes. This RCT used the recommendation of fentanyl at either 1-5mcg/kg/hr or 0.5-4mcg/kg/dose every 2-4 hours.</td>
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