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Preemptive Pregabalin in Children and Adolescents
Undergoing Posterior Instrumented Spinal Fusion A
Double-Blinded, Placebo-Controlled, Randomized Clinical Trial

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1 **Abstract** 261 words (max, 325)

2 **Background:**

3 Pregabalin as part of a multimodal pain management regimen has been shown to reduce opioid
4 consumption after spinal surgery in adults, but not in adolescents. Pregabalin has been found to
5 have neuroprotective effects and could therefore have positive impact on pain after spinal deformity
6 surgery. We conducted a randomized, double-blind, placebo-controlled clinical trial with pregabalin
7 on pediatric patients undergoing spinal fusion.

8 **Methods:**

9 Adolescents **with adolescent idiopathic scoliosis, Scheuermann kyphosis and spondylolisthesis,**
10 aged 10 to 21 years, scheduled for posterior spinal fusion with all pedicle screw instrumentation
11 were randomized to receive preoperatively and five days after surgery either pregabalin 2mg/kg
12 twice daily or placebo. The primary outcome was total opioid consumption and was measured using
13 patient-controlled analgesia. Postoperative pain scores and opioid adverse effects were evaluated.

14 **Results:**

15 Sixty-three patients out of 77 eligible were included and analyzed. Cumulative oxycodone
16 consumption per kilogram did not differ between the study groups during the first 48 hours
17 postoperatively, median (95% confidence interval) 1.44 mg/kg (1.32 - 1.67) in the pregabalin vs.
18 1.50 mg/kg (1.39 - 1.79) in the placebo group, $p=0.433$. **Subgroup analysis with only AIS**
19 **patients showed the same result, mean (95% confidence interval) 1.45 mg/kg (1.24, 1.65) in**
20 **pregabalin group and 1.59 mg/kg (1.37, 1.82) in placebo group.** Total oxycodone consumption
21 per hour (mg/kg/h) was not different between the groups over the time points ($p=0.752$). The
22 postoperative pain scores did not differ statistically between the study groups ($p=0.196$).

23 **Conclusions:**

1 The use of perioperative pregabalin does not reduce the opioid consumption or affect the pain
2 scores in adolescents after posterior spinal fusion surgery.

3 Level of evidence: I

4 **Keywords:** pregabalin; multimodal pain management; pediatric patients; spinal surgery;
5 adolescent idiopathic scoliosis

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1 Introduction

2 Posterior spinal fusion represents the fifth most common surgical procedure in the United States¹. In
3 the pediatric population spinal deformities are the main indication for posterior instrumented spinal
4 fusion. Extensive spinal muscle exposure, segmental pedicle screw instrumentation and arthrodesis
5 are effective in aiming at three-dimensional correction of adolescent idiopathic scoliosis².
6 Postoperatively the pain management can be challenging and therefore a multimodal approach is
7 often necessary. In recent years, the concerns regarding increasing postoperative opioid
8 consumption and the negative effects of prolonged opioid use has made the opioid-sparing pain
9 management even more important³. Orthopaedic surgeons accounts for a major part of the
10 prescribed postoperative opioids.

11 In adults undergoing spinal surgery, pre- and postoperative pregabalin has been shown
12 to reduce postoperative pain more effectively than placebo and gabapentin and, has shown opioid-
13 sparing effects⁴⁻⁸. Pregabalin has also showed neuroprotective properties in animal studies⁹.
14 Gabapentinoids are recommended by the American Pain Society as components of multimodal
15 postoperative pain therapy in adults^{10, 11}.

16 To our best knowledge, no studies have been performed in children using
17 perioperative pregabalin for postoperative pain after spinal surgery. Nevertheless, though widely
18 used for prevention of postoperative pain in adults, pregabalin lacks regulatory-approval for use in
19 children and adolescents. The safety and efficacy of pregabalin in children has been evaluated in
20 two studies. One study investigated the efficacy of pregabalin in children aged 12 to 17 years as a
21 treatment for fibromyalgia¹². In the study by Mann et al, the safety of pregabalin was evaluated in
22 children with refractory partial seizures. Doses up to 10mg/kg/day in children aged 1 month to 16
23 years, and at doses up to 15 mg/kg/day in those aged <6 years, demonstrated acceptable safety and
24 tolerability¹³.

We aimed to evaluate the effects of preemptive pregabalin on the **immediate** postoperative pain and opioid consumption in adolescents undergoing posterior spinal fusion using a randomized, double-blind, placebo-controlled study design. We hypothesized that perioperative pregabalin would reduce the postoperative opioid consumption with reduced pain scores.

1 Materials and Methods

2 This study was approved by Ethics Committee of the Hospital District and the National Agency of
3 Medicines. A written informed consent from each patient and their parents was obtained. The
4 clinical trial has been registered in the public trials registry, ClinicalTrials.gov (NCT02464813).
5 Ilkka Helenius assigned as principal investigator and date of registration 01.06.2015. This
6 manuscript adheres to the applicable CONSORT guidelines. The study has been carried out in
7 accordance with World Medical Association Declaration of Helsinki.

8 Study sample

9 Sixty-four adolescents (31 randomly allocated to control group with placebo and 33 to active
10 treatment group with pregabalin) undergoing instrumented spinal fusion surgery between August
11 2015 and September 2018 gave their consent to participate in the study. Inclusion criteria were
12 adolescents (age 10 - 21 years) scheduled for posterior spinal surgery with all pedicle screws
13 instrumentation for adolescent idiopathic scoliosis (AIS), **high-grade** spondylolisthesis or
14 Scheuermann kyphosis (SK). The patients had ASA physical status II or less. Exclusion criteria
15 were other spinal pathology, neurological development delay, other associated medical condition
16 (neuromuscular scoliosis), need for anterior surgery or vertebral column resection, and preoperative
17 opioid use. All procedures were performed by the same experienced orthopaedic spine surgeon. The
18 primary outcome variable of the study was cumulative oxycodone consumption during the first 48
19 postoperative hours and total hourly oxycodone consumption. The secondary outcome variables
20 included postoperative pain (verbal numeric rating scale 0-10) during the first 48 hours, use of
21 rescue analgesia, and length of hospital stay.

22 Study design

23 The randomization to the study groups (1:1) was done by the Department of Pharmacy at our
24 university hospital based on a predetermined list with blocks of 20 patients. The Department of

Pharmacy manufactured the study drugs and the drugs were delivered to the ward for each study subject according to randomization. The investigators, patients, parents, nursing staff, and surgeons were blinded to group assignment. Patients in the pregabalin group received an oral 2 mg/kg dose of pregabalin rounded up to next 25mg on the preoperative evening, 12 hours before induction of anesthesia. The patients received the second dose preoperatively approximately two hours before induction of anesthesia. Maximum dose of pregabalin for any patient was 150 mg b.i.d. Patients in the placebo group received the same amount of similar looking capsules at similar timing.

Induction and maintenance of anesthesia was standardized. Anesthesia was induced and maintained with propofol-TCI (**target-controlled infusion**) and remifentanyl-TCI titrated to maintain the bispectral index (BIS) within predetermined limits¹⁴⁻¹⁶. Dexmedetomidine was used in all patients for additive hypnosis and analgesia. All patients received betamethasone 0.2 mg/kg, vancomycin 10 mg/kg and cefuroxime 60 mg/kg as antibiotic prophylaxis and tranexamic acid 30 mg/kg IV (max 1500mg). Tranexamic acid administration was continued with an infusion rate of 10 mg/kg/h until wound closure. Vital signs were monitored and kept within the following limits: mean arterial pressure between 65-75 mmHg with noradrenaline infusion if needed, body temperature 36.0 – 37.0 °C and BIS between 40-60. Neurophysiological measurements were done every 20 min and at specific time points. In order to evaluate the safety of the study intervention, a data analysis of the neurophysiological measurements was performed after recruitment of the first 31 patients and the results were published¹⁷.

The patients were mobilized using a standardized protocol. On the first postoperative day the patients were requested to stand up and to walk a couple of steps, and on the second postoperative day the patients were encouraged to walk on the ward. Urinary catheter was routinely removed on the second postoperative day and the residual volume was measured using an ultrasound.

1 Surgical technique

2 All patients were operated using a posterior approach only. Pedicle screws were inserted at every
3 level and direct vertebral column derotation (Solera 6.0, Medtronic Spinal and Biologics, Memphis,
4 TN, USA) was used to correct adolescent idiopathic scoliosis¹⁸, posterior column osteotomy when
5 needed. Cantilever maneuver with posterior column osteotomies was used to correct Scheuermann
6 kyphosis¹⁹. **Patients with spondylolisthesis had wide nerve root (L5, S1) and cauda equine**
7 **decompression followed by full instrumented reduction of their spondylolisthesis.**

8 Transforaminal lumbar intercorporeal fusion cage was inserted in addition to standard posterolateral
9 spinal arthrodesis. A single subfascial drain (Hemovac Ch 14; Zimmer, Warsaw, Indiana) was
10 routinely inserted and removed at 24 hours postoperatively.

11 Pain management

12 Before surgery, all patients were instructed on the use of the patient-controlled analgesia (PCA)
13 system (CADD-Legacy PCA Pump Model 6300; Smiths Medical). Standard oxycodone PCA was
14 initiated in the postoperative care unit (ICU), with on demand oxycodone-bolus of 0.03mg/kg/dose
15 every 10 minutes and an hourly maximum of 0.1 mg/kg, with no basal infusion. An ICU nurse gave
16 boluses from the PCA when needed, based on signs as tachycardia and hypertension, until the
17 patient was able to use the device him/herself. **The use of patient-controlled analgesia device was**
18 **carefully planned by the attending anesthesiologist and the device was not reset during the 48-**
19 **hour period of use. The device shows the exact amount of oxycodone the patient has received.**
20 Oxycodone PCA was continued for 48 hours in all patients. All patients received oral paracetamol
21 20mg/kg x 3. Oral etoricoxib 2-3mg/kg x 1 was used as rescue analgesia. Rescue analgesia was
22 initiated if the patient reported high pain scores despite appropriate PCA. Oral opioid analgesics
23 were initiated 48h after end of surgery. All patients received lactuloses 20ml x 2 and
24 sodiumpicosulfate 10 drops x 1 for prophylaxis of constipation. All adverse effects were registered
25 and treated appropriately according to normal clinical practice.

1 Study variables

2 Data collected included vital signs, pain scores (verbal numeric rating scale 0-10) in rest and in
3 movement²⁰, sedation scores, opioid consumption, and adverse effects (specifically nausea,
4 dizziness, constipation, and pruritus). Opioid consumption was recorded and analyzed in 8 h
5 intervals (mg/kg/h) and as cumulative amount per day (mg/kg). Demographic data collected
6 included age, weight, height, body mass index, and gender. **Back pain and radiculopathy were**
7 **evaluated using the SRS-24 outcome questionnaire and pain drawing preoperatively.**
8 Orthopaedic data included Lenke classification²¹, preoperative and postoperative Cobb angle²²,
9 intraoperative blood loss, and levels fused. Wound infection and need for re-operation were
10 registered.

11 If the patient reported signs of neural injury or neuropathic pain after surgery,
12 pregabalin treatment was initiated and study drugs withdrawn.

13 Statistical analysis

14 Statistical comparison was performed using the intention-to-treat analysis principle. Baseline
15 characteristics and length of hospital stay were compared with Mann-Whitney U-test (except gender
16 with Chi-Square test) and number of subjects having adverse events and need for rescue analgesia
17 with Chi-Square test. Cumulative oxycodone consumption at 24 hours and at 48 hours (mg/kg) was
18 analyzed using covariance analysis where number of level fused was handled as covariate and
19 group was categorical factor. The analysis of the oxycodone consumption in mg/kg/h at the five
20 time points was analyzed using linear mixed model. To study whether pain scores changes over
21 time, a linear mixed model with repeated measures was used, including one within-factor (time),
22 and several between-factor (group, levels fused). Compound symmetry covariance structure was
23 used for time. Normal distribution of the variables was evaluated from studentized residuals
24 visually together with Shapiro-Wilk test. Significance level was set to 0.05 (two-tailed). The

analyses were performed using SAS System, version 9.4 for Windows (SAS Institute Inc., Cary, NC, US). The sample-size calculation was based on a study by Rusy et al. in similar set-up as the current study²³. It shows that a sample size of 30 subjects per group is required to detect 30% difference in opioid use between the groups at an alpha-level of 0.05 and a power of 0.80. The mean daily use of opioids in patients receiving saline as 60mg and standard deviation (SD) 30mg was taken from our previous pilot study.

Results

Seventy-seven consecutive patients were evaluated for enrollment [Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram]. Sixty-four of these patients gave their consent for participation in the study (83%). After completion of the study protocol, one patient was excluded from final data due to not fulfilling the inclusion criteria (excision of osteoid osteoma). Pregabalin group consisted of 32 patients (25 AIS, 4 SK, and 3 Spondylolisthesis). Placebo group consisted of 31 patients (26 AIS, 5 Spondylolisthesis). There were no statistical differences between the two groups regarding demographic and clinical characteristics as presented in Table I. The groups were also similar regarding surgical characteristics (Table I). There were no deep wound infections or early re-operations in either group.

There was no significant difference between the two groups measured in cumulative oxycodone consumption per kilogram for 48 hours after end of surgery adjusted for levels fused. The median consumption in mg/kg (95%CI) for pregabalin group 1.44 (1.32 - 1.67) vs placebo group 1.50 (1.39 - 1.79), $p=0.433$ (Table II). We also calculated the hourly oxycodone consumption in mg/kg/h, comparing the groups over time showed no statistical difference, $p=0.752$ (Fig. 2). No statistical difference existed in the use of rescue analgesia between the groups ($p=0.200$). **The patient's total oxycodone consumption during the hospital stay was registered. The difference between groups was not statistically significant, mean (95%CI) pregabalin 2.90 mg/kg (2.75, 3.51) vs placebo 3.07 mg/kg (2.96, 3.88), $p=0.353$. None of the patients were discharged with an opioid prescription**

The postoperative pain scores at rest (one hour to 48 hours) did not differ statistically between the study groups over time ($p=0.196$) as shown in Figure 2. Neither did the pain scores in movement differ statistically between groups ($p=0.244$).

A subgroup analysis with only AIS patients was performed. These results were similar to previous results. No differences between groups were found regarding opioid consumption or pain scores (Table III). There was a significant correlation between preoperative pain and opioid consumption at 24h and 48h after surgery ($r = -0.35$, $p = 0.019$).

No differences were found between the groups for any measured opioid-related adverse effects. These were somnolence, respiratory depression, nausea and vomiting and pruritus (Table II).

Three (2 spondylolisthesis, 1 AIS) patients in the pregabalin group and three (2 spondylolisthesis, 1 AIS) patients in the placebo group reported signs of neuropathic pain immediately postoperatively. For these patients pregabalin treatment was initiated and study drugs withdrawn, or pregabalin treatment was initiated after study drug treatment had ended. The signs of neuropathic pain were relieved in all these patients during follow-up.

No statistical difference was found in the length of hospital stay between pregabalin and placebo groups, reported in mean (days) and range, 6.5 (4 - 10) vs 6.8 (5 - 9), $p = 0.348$.

Discussion

Pregabalin is a new-generation gabapentinoid, which originally was developed for use as an anti-epileptic drug. Pregabalin has a superior pharmacokinetic profile and is a more potent analgetic in neuropathic pain compared with gabapentin²⁴. Pregabalin binds with high affinity to the $\alpha 2\delta$ – subunit of presynaptic voltage-dependent calcium-channels which are distributed in the peripheral and central nervous system. The activation of these calcium-channels results in a reduction in the release of neurotransmitters. This is thought to explain its antinociceptive effects^{25, 26}. Pregabalin has many features that promote its use preoperatively, particularly preemptive analgesia and a potential neuroprotective effect⁹⁻¹¹. According to a recently published systemic review of the efficacy and safety of gabapentin and pregabalin for pain in children and adolescents the evidence-based data supporting the use of these drugs is very sparse²⁷. In the adult population preoperative pregabalin has been shown in many studies to reduce postoperative pain and opioid consumption in patients undergoing posterior spinal fusion⁴⁻⁸.

There are two randomized, placebo-controlled studies published evaluating the use of gabapentin in pediatric spinal fusion patients. In the study from Rusy et al, 59 pediatric spinal fusion patients were randomized to receive preoperative gabapentin 15 mg/kg or placebo and the medication was continued for 5 days²³. This study showed a reduction in morphine consumption postoperatively compared to the placebo group. In the other study the patients were given one single preoperative dose of gabapentin 600 mg one hour before surgery²⁸. A single preoperative dose of gabapentin did not show a difference in opioid consumption in adolescents undergoing scoliosis surgery.

In our study it seems that pregabalin cannot add value to the multimodal pain management in our patients undergoing major spinal surgery. An extensive part of our intraoperative anesthetic management aims to reduce postoperative pain. We used

dexmedetomidine infusion as part of the total intravenous anesthesia. Dexmedetomidine has in previous studies shown to have analgesic effects, although not supported by all studies²⁹⁻³¹. All patients received betamethasone at induction, with an analgesic and antinociceptive effect³². The additive effect of this multimodal pain management probably reduces the added value of pregabalin, and the opioid-sparing effect does not seem to exist. **The outcomes of this study are based on the hospital stay and thus the long-term effects of pregabalin remains unclear.** The effect of perioperative pregabalin on the persistent postoperative pain remains to be evaluated.

The negative findings of our study cannot be explained by under dosing. During planning the design of this study, we intentionally decided to use a relatively high dose of pregabalin, in order to receive the maximum effect of the drug (2-3mg/kg twice daily). The commonly used dosage of pregabalin in neuropathic pain is 1-2mg/kg twice daily.

One may ask, whether the sample size was too small to show a statistical difference. **We chose an effect size of 0.60 in the statistical power calculation with typical significance set at 0.05 and study power of 0.80, which resulted into 30 children per group. Based on the current findings we observed a maximum effect size ~0.25, which is considered as small and not clinically significant³³. A bigger sample size would give more power, but such small difference in opioid consumption cannot be considered clinically relevant.**

Another limitation of our study is the somewhat heterogenic sample with three pediatric conditions. Since AIS, SK, and high-grade spondylolisthesis represent the three most common pediatric spinal disorders requiring spinal fusion, all three were included in the current study. The instrumented reduction of spondylolisthesis has a much greater risk of postoperative neuropathy, compared to AIS and SK which require treatment for generalized spinal pain. We therefore performed a subgroup analysis with adolescent idiopathic scoliosis patients and the results were the same. It would have been interesting to evaluate whether

pregabalin was helpful in patients with spondylolisthesis as half of them developed neuropathic pain postoperatively. However, the small number of spondylolisthesis patients prevents us to answer this question in our study.

In conclusion, perioperative pregabalin did not reduce the postoperative opioid consumption or pain scores in adolescents undergoing posterior spinal fusion compared to placebo group.

1 **AUTHORS' CONTRIBUTIONS**

2 Substantial contribution to conception and design: LH, OP, EL, TM, IH.

3 Acquisition of data: LH, HO, ML, OP, IH.

4 Analysis and interpretation of data: LH, HO, EL

5 Drafting the article: LH

6 Critically revising the article: HO, ML, OP, EL, TM, IH

7 Final approval: LH, HO, ML, OP, EL, TM, IH.

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References (max 40)

1. Healthcare Cost and Utilization Project (HCUP). Most common operations during inpatient stays. 2017. <https://www.hcup-us.ahrq.gov/faststats/NationalProceduresServlet>.
2. Lehman RA Jr, Lenke LG, Keeler KA, et al. Operative treatment of adolescent idiopathic scoliosis with posterior pedicle screw-only constructs: minimum three-year follow-up of one hundred fourteen cases. *Spine (Phila Pa 1976)*. 2008 Jun 15;33(14):1598-604.
3. Sabatino MJ, Kunkel ST, Ramkumar DB, Keeney BJ, Jevsevar DS. Excess Opioid Medication and Variation in Prescribing Patterns Following Common Orthopaedic Procedures. *J Bone Joint Surg Am*. 2018 Feb 7;100(3):180-188.
4. Khurana G, Jindal P, Sharma JP, Bansal KK. Postoperative pain and long-term functional outcome after administration of gabapentin and pregabalin in patients undergoing spinal surgery. *Spine (Phila Pa 1976)*. 2014 Mar 15;39(6):E363-8.
5. Kim JC, Choi YS, Kim KN, Shim JK, Lee JY, Kwak YL. Effective dose of peri-operative oral pregabalin as an adjunct to multimodal analgesic regimen in lumbar spinal fusion surgery. *Spine (Phila Pa 1976)*. 2011 Mar 15;36(6):428-33.

6. Yu L, Ran B, Li M, Shi Z. Gabapentin and pregabalin in the management of postoperative pain after lumbar spinal surgery: a systematic review and meta-analysis. *Spine (Phila Pa 1976)*. 2013 Oct 15;38(22):1947-52.
7. Giancesello L, Pavoni V, Barboni E, Galeotti I, Nella A. Perioperative pregabalin for postoperative pain control and quality of life after major spinal surgery. *J Neurosurg Anesthesiol*. 2012 Apr;24(2):121-6.
8. Fujita N, Tobe M, Tsukamoto N, Saito S, Obata H. A randomized placebo-controlled study of preoperative pregabalin for postoperative analgesia in patients with spinal surgery. *J Clin Anesth*. 2016 Jun;31:149-53.
9. Ha KY, Kim YH, Rhyu KW, Kwon SE. Pregabalin as a neuroprotector after spinal cord injury in rats. *Eur Spine J*. 2008 Jun;17(6):864-72.
10. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of Postoperative Pain: A Clinical Practice Guideline From the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain*. 2016 Feb;17(2):131-57.
11. Liu B, Liu R, Wang L. A meta-analysis of the preoperative use of gabapentinoids for the treatment of acute postoperative pain following spinal surgery. *Medicine (Baltimore)*. 2017 Sep;96(37):e8031.

12. Arnold LM, Schikler KN, Bateman L, et al; Pregabalin Adolescent Fibromyalgia Study Group. Safety and efficacy of pregabalin in adolescents with fibromyalgia: a randomized, double-blind, placebo-controlled trial and a 6-month open-label extension study. *Pediatr Rheumatol Online J*. 2016 Jul 30;14(1):46.
13. Mann D, Liu J, Chew ML, et al. Safety, tolerability, and pharmacokinetics of pregabalin in children with refractory partial seizures: A phase 1, randomized controlled study. *Epilepsia*. 2014 Dec;55(12):1934-43.
14. Kataria BK, Ved SA, Nicodemus HF, et al. The pharmacokinetics of propofol in children using three different data analysis approaches. *Anesthesiology*. 1994 Jan;80(1):104-22.
15. Minto C, Schnider T, Egan T, et al. Influence of age and gender on the pharmacokinetics of remifentanyl. *Anesthesiology*. 1997 Jan;86(1):24-33.
16. Rigouzzo A, Girault L, Louvet N et al. The relationship between bispectral index and propofol during target-controlled infusion anesthesia: a comparative study between children and young adults. *Anesth Analg*. 2008 Apr;106(4):1109-16.
17. Helenius L, Puhakka A, Manner T, Pajulo O, Helenius I. Preoperative pregabalin has no effect on intraoperative neurophysiological monitoring in adolescents undergoing posterior spinal fusion for spinal deformities: a double-blind, randomized, placebo-controlled clinical trial. *Eur Spine J*. 2018 Feb;27(2):298-304.

18. Mattila M, Jalanko T, Helenius I. En bloc vertebral column derotation provides spinal derotation but no additional effect on thoracic rib hump correction as compared with no derotation in adolescents undergoing surgery for idiopathic scoliosis with total pedicle screw instrumentation. *Spine (Phila Pa 1976)*. 2013 Aug 15;38(18):1576-83.
19. Geck MJ, Macagno A, Ponte A, Shufflebarger HL. The Ponte procedure: posterior only treatment of Scheuermann's kyphosis using segmental posterior shortening and pedicle screw instrumentation. *J Spinal Disord Tech*. 2007 Dec;20(8):586-93.
20. von Baeyer CL. Numerical rating scale for self-report of pain intensity in children and adolescents: recent progress and further questions. *Eur J Pain*. 2009 Nov;13(10):1005-7.
21. Lenke LG, Betz RR, Harms J, et al. Adolescent idiopathic scoliosis: a new classification to determine extent of spinal arthrodesis. *J Bone Joint Surg Am*. 2001 Aug;83(8):1169-81.
22. Cobb JR. Outline for the study of scoliosis. *Instr Course Lect* 1948; 5: 261-75.
23. Rusy LM, Hainsworth KR, Nelson TJ, Czarnecki ML, Tassone JC, Thometz JG, Lyon RM, Berens RJ, Weisman SJ. Gabapentin use in pediatric spinal fusion patients: a randomized, double-blind, controlled trial. *Anesth Analg*. 2010 May 1;110(5):1393-8.
24. Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. *Clin Pharmacokinet*. 2010 Oct;49(10):661-9.

25. Woolf CJ, Chong MS. Preemptive analgesia--treating postoperative pain by preventing the establishment of central sensitization. *Anesth Analg.* 1993 Aug;77(2):362-79.
26. Tiippana EM, Hamunen K, Kontinen VK et al. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg.* 2007 Jun;104(6):1545-56.
27. Egunsola O, Wylie CE, Chitty KM, Buckley NA. Systematic Review of the Efficacy and Safety of Gabapentin and Pregabalin for Pain in Children and Adolescents. *Anesth Analg.* 2019 Apr;128(4):811-819.
28. Mayell A, Srinivasan I, Campbell F et al. Analgesic effects of gabapentin after scoliosis surgery in children: a randomized controlled trial. *Paediatr Anaesth.* 2014 Dec;24(12):1239-44.
29. Naik BI, Nemergut EC, Kazemi A, Fernández L, Cederholm SK, McMurry TL, Durieux ME. The Effect of Dexmedetomidine on Postoperative Opioid Consumption and Pain After Major Spine Surgery. *Anesth Analg.* 2016 May;122(5):1646-53.
30. Hwang W, Lee J, Park J, Joo J. Dexmedetomidine versus remifentanyl in postoperative pain control after spinal surgery: a randomized controlled study. *BMC Anesthesiol.* 2015 Feb 24;15:21.

- 1
- 2 31. Bellon M, Le Bot A, Michelet D, Hilly J, Maesani M, Brasher C, Dahmani S. Efficacy of
- 3 Intraoperative Dexmedetomidine Compared with Placebo for Postoperative Pain
- 4 Management: A Meta-Analysis of Published Studies. *Pain Ther.* 2016 Jun;5(1):63-80.
- 5
- 6 32. Wang F, Shi K, Jiang Y, Yang Z, Chen G, Song K. Intravenous glucocorticoid for pain
- 7 control after spinal fusion: A meta-analysis of randomized controlled trials. *Medicine*
- 8 (Baltimore). 2018 May;97(20):e10507.
- 9
- 10 33. Lochner HV, Bhandari M, Tornetta P 3rd. Type-II error rates (beta errors) of randomized
- 11 trials in orthopaedic trauma. *J Bone Joint Surg Am.* 2001 Nov;83(11):1650-5.
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- 1 Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.
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- 3 Figure 2. Oxycodone consumption per hour, data shown in mean and standard deviation.
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- 5 Figure 3. Verbal numerical pain rating, shown in mean and standard deviation.