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Preemptive and Preventive Analgesia in Different Paediatric Surgical Settings: A Systematic Review of Prospective Randomized Controlled Trials

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Abstract

The effect of preemptive and preventive analgesia in children undergoing surgical procedures has not been adequately studied. The aim of this review was to investigate literature regarding the effectiveness of preemptive and preventive analgesia in postoperative pain relief in children undergoing surgery according to the type of both, the surgical procedure and the analgesic intervention, and the analgesic or adjuvant used. Our critical review of prospective randomized controlled trials identified 77 studies; 39 were referred to head and neck surgeries, 31 to urological and lower abdominal procedures, 6 to orthopaedics and one to all the above types of operations. Our literature review demonstrated that the preemptive administration of ketamine (intravenous, topical, caudal) before surgical incision in children undergoing tonsillectomy or urological surgeries probably can enhance postoperative analgesia quality and reduce analgesic demands and it may also be recommended as an alternative safe option to opioids. On the contrary, preventative administration of ketamine in Orthopaedic procedures has not been shown to be beneficial in the management of acute postoperative pain. Dexmedetomidine seems to be a promising adjunct to provide excellent postoperative analgesia especially in urological and lower abdominal operations, given intravenously or caudally, preoperatively. The increasing interest on dexmedetomidine preemptive effects was justified in our review. Literature findings are supporting regarding the use of caudal administration of clonidine and neostigmine. Studies on other kinds of adjuvants in children are very limited and further investigation should be done.

Keywords: Preemptive; Preventive; Analgesia; Children; Postoperative pain

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Introduction

The increasing prevalence of paediatric surgical procedures demands a more thorough understanding of the post-surgical recovery in children. In 2012 a cohort study was performed in the United States in order to determine annual frequencies and types of in-hospital surgical procedures (excepting ambulatory surgeries) performed on children. They evaluated 3 different years (2003, 2006, 2009) and they showed that approximately 450,000 children under 18 years of age are admitted for surgery as inpatients annually. The majority of surgical admissions classified as gastrointestinal, orthopaedic, or urological [1]. Furthermore, recent data showed that the severity and duration of postoperative pain in children undergoing the above surgical procedures, such as tonsillectomy, orchidopexy, or inguinal hernia repair, should not be underestimated [2]. Pain is a strong factor associated not only with postoperative children's recovery but even with the onset of a problematic behaviour after hospitalization [3]. These results are useful to explain the increasing emphasis on improving postoperative pain control in young population.

Pain is an unpleasant sensation associated with sensory and emotional experiences that can cause potential or actual tissue damage [4]. Postoperative pain takes place as a consequence of tissue trauma and may guide to physical, cognitive, and emotional discomfort. In addition, severe acute pain is a risk factor for the development of chronic pain [5]. Therefore, postoperative pain and its management is a crucial issue between anaesthesia providers. The concepts of preemptive and preventive analgesia appeared last decades in order to decrease postoperative pain intensity, analgesics' consumption and long-term pain sensitization [6]. Preemptive analgesia focuses on postoperative pain control and the prevention of central sensitization and chronic neuropathic pain by providing analgesia administered preoperatively, but not after surgical incision [6]. On the other hand, preventive analgesia includes multimodal preoperative and postoperative analgesic therapies

and results in decreased postoperative pain and less postoperative consumption of analgesics [6]. Finally, multimodal analgesia consists of the administration of two or more drugs that act by different mechanisms for providing analgesia [7].

Postoperative pain relief in children is a challenge. Many studies have been performed trying to evaluate different postoperative pain management strategies in children. These strategies include systemic analgesia or locoregional analgesia including central regional blockade (mainly caudal or lumbar), plexus and peripheral nerve blocks and wound infiltration [8]. Systemic analgesia is usually given orally, intravenously or by rectal. Many drugs have been used as part of a multimodal approach for pain relief, such as acetaminophen, Non-Steroidal Anti-Inflammatory agents (NSAIDs), opioids and adjuvants. Drugs often used as adjuvants given intravenously in pediatrics are: ketamine (an N-Methyl-D-Aspartate [NMDA] receptor antagonist), magnesium and dexmedetomidine (an a2 adrenergic agonist) [9]. Local anaesthetics most commonly used for central and peripheral regional blockades and local blocks are lidocaine, bupivacaine and ropivacaine administered alone or in combination with clonidine (an a2 adrenergic agonist), neostigmine or ketamine [10]. In addition, the timing of administration of analgesic drugs or application of regional techniques in relation to the surgical incision is also an important factor that may affect the efficacy of postoperative pain control.

Systematic reviews on the efficacy and safety of all the above interventions in paediatrics are still lacking. Therefore, the present review is aimed at investigating the existing literature regarding the effectiveness of preemptive and preventive analgesia for postoperative pain relief in children, according to the surgical procedure, the type of the analgesic intervention and the analgesic or adjuvant used.

Materials and Methods

Bibliographical search and analysis

The National Library of Medicine's PubMed database, the cochrane library and Scopus were all searched for studies investigating the effectiveness of preemptive/preventive analgesia in children undergoing surgery, up to September of 2018 with no time limitation. Additional studies of selected publications were identified from hand searches of the bibliographies and on Google scholar. The Medical Subject Heading (MeSH) terms used to review the literature were preemptive, preventive, analgesia, children, and pain, postoperative. Articles identified by the search were analyzed by 2 physicians to verify their relevance and determine eligibility with the particular study. All the trials were reviewed independently by each of the authors. When conflicting results were found, the article was checked by a third anaesthesiologist.

Inclusion criteria

Studies considered of suitable design for inclusion were only prospective Randomized Controlled Trials (RCTs) in order to lessen biases. Articles were limited only in human participants. We also limited our review to studies involving children (<18 years old) undergoing surgical procedures. Studies that were included investigated the use of analgesia administered by any route, in any dosage to treat pain postoperatively as part of preemptive or preventive analgesia.

Exclusion criteria

Cohort or observational studies, data from abstracts, case reports, nonsurgical settings, or from experimental studies in animals were excluded from the analysis. Also, retrospective analyses or studies without randomization were not included to avoid any potential bias.

Outcomes

This review is aimed to evaluate the effectiveness of preemptive and preventive analgesia in postoperative pain relief in children undergoing surgical procedures according to the type of the surgical procedure, the type of the analgesic intervention, the analgesic or adjuvant used and the time that the analgesic technique applied in relation to the surgical incision. The primary outcome of our analysis is postoperative pain relief, in terms of pain intensity (measured with pain scales) and/or postoperative analgesic consumption.

Identification of trials

The systematic literature search using the selected medical terms yielded 158 relevant studies. Eleven studies were excluded because they were duplicated. Eighteen studies were excluded as they were referred in adults and 40 more excluded because of inappropriate study design (they appeared to be reviews, meta-analysis, cohort, observational studies or case reports). Therefore, a total of 89 records were further assessed for eligibility and of these 12 were excluded from our research for other reasons, such as not measuring pain intensity or analgesic consumption. Finally, only 77 trials met our inclusion criteria and are investigated in this review article. The trial flow is shown in Figure 1.

Studies' characteristics

All studies were performed with adequate sample size, in particular the numbers within treatment groups ranged from 20 to 241 subjects. The duration of the postoperative patient follow-up in the trials varied from 6 h to 5 days.

The evaluation of pain intensity was assessed in all the selected studies with validated scales measuring pain such as the Visual Analogue Scale (VAS), the Numerical Rating Scale (NRS), the Observational Pain Scale (OPS), the Children's Hospital of Eastern

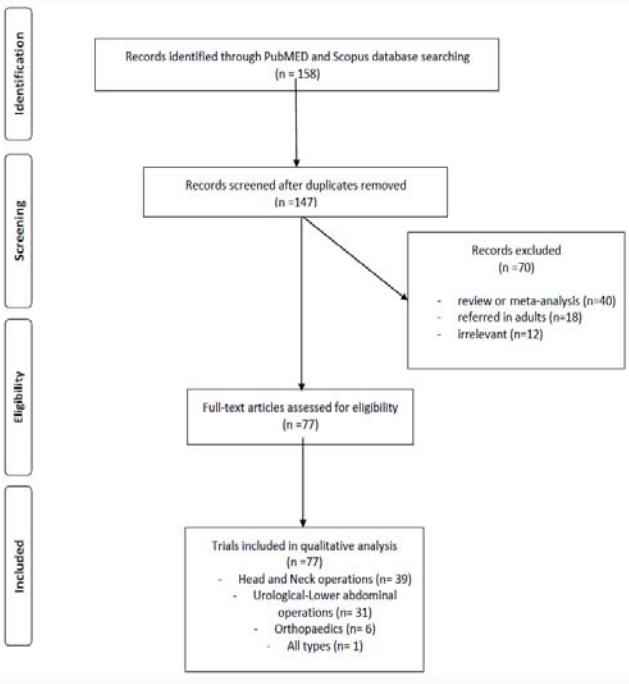

Figure 1: Flow diagram.

Table 1: RCTs investigating the preemptive/preventive analgesic effect of different agents in children undergoing Head and Neck surgical procedures.

NR	Author/ Year	Ages	Sample size/Groups	Surgery/ Protocol/ Time of drug administration	Postoperative pain intensity	Analgesic consumption
CLONIDINE						
11	Giannoni C et al. 2001	3-15 years	N= 64 Saline Group, n= 21 Group Rop, n=21 Group Rop+Clo, n=22	Tonsillectomy Topical injection of: Saline Group: N/S *vs.* Group Rop: Ropivacaine + N/S *vs.* Group Rop+Clo: Ropivacaine + Clonidine 1µg/kg Preoperatively	Reduced VAS score on PO day 0 in the Rop and Rop+clo treated groups compared with the saline group (p<0.05). Reduced pain on PO days 3-5 in the Rop+clo treated group	NS in cumulative codeine use between the groups for the first 3 PO days. Reduced cumulative codeine use for the Rop+Clon treated group on day 5 (p<0.05).
12	Moss JR et al. 2011	3-17 years	N=120 Group 1, n=40 Group 2, n=40 Group 3, n=40	Tonsillectomy Topical injection of: Group 1: N/S *vs.* Group 2: Lidocaine + Bupivacaine *vs.* Group 3: Lidocaine + Bupivacaine + Clonidine 25µg Preoperatively	Reduced pain on POD 3 in the Placebo group (p=0.02)	NS in total number of analgesic doses on PODs 1, 3, 5, and 7 between the randomization groups. NS in the median numbers of analgesic doses.
13	Bergendahl HT et al. 2004	1-11 years	N=100 Group M, n=52 Group C, n=48	Tonsillectomy Rectal premedication Group M: Midazolam + Atropine *vs.* Group C: Clonidine 5 µg/ kg + Atropine	Reduced OPS scores the first 0-2 hours in Group C (p=0.011)	
KETAMINE						
Ketamine IV						
14	Osman N. Aydin et al. 2007	5-15 years	N=90 Saline Group, n=30 Preventive Group, n=30 Ketamine Group, n=30	Tonsillectomy Saline Group: preoperative IV N/S *vs.* Preventive Group: preoperative IV Ketamine 0.5 mg/kg and intraoperative Ketamine 6 µg/kg/min continuous infusion *vs.* Ketamine Group: IV Ketamine 0.8 mg/kg during bleeding control	Reduced verbal pain scale scores in the pain preventive group, the early PO period, in the 4th and 6th hour (p<0.05). Reduced level of pain in the preventive group compared with the groups in the immediate PO period (p=0.001).	Reduced number of patients required Tramadol at the first hour in the preventive group (p<0.05). Reduced Tramadol requirements during the first 6 hours in preventive group than in the other groups (p=0.003).
15	Inanoglu K. et al. 2009	2 - 12 years	N=90 Group I, n=30 Group II, n=30 Group III, n=30	Tonsillectomy Group Group I: N/S IV + peritonsillar *vs.* Group II: IV N/S + peritonsillar Bupivacaine *vs.* Group III: IV Ketamine 0.5 mg/kg + peritonsillar Bupivacaine Preoperatively	Reduced Pain (evaluated mCHEOPS) in Group III at all time intervals (15 min and 1, 4, 12, 16, and 24 h postoperatively) compared with Group I (p<0.05). Reduced Pain scores in group III compared with group II at all time intervals except at 15th min (p<0.05).	Reduced analgesic requirements in the ketamine group (p<0.05). Increased time to first analgesia in the ketamine group (p<0.05). Reduced rescue analgesia (fentanyl citrate, oral acetaminophen) in group III (p<0.05).
16	Eghbal MH et al. 2013	5–15 years	N=66 Control Group, n=33 Ketamine Group, n=33	Tonsillectomy Control Group: IV N/S *vs.* Ketamine Group: IV Ketamine 0.25 mg/kg Preoperatively	Reduced Pain score at all hours in the ketamine group than the control group (p<0.05) measuring for 6 hours.	Reduced requirements for intravenous paracetamol in the ketamine group for 6 h (p= 0.0036).
17	Kimiaei Asadi H et al. 2016	3 - 12 years	N=98 Ketamine group, n=49 Control group, n=49	Tonsillectomy Ketamine Group: Ketamine 0.25 mg/ kg, 15 min *vs.* Control group: N/S Before the end of the surgery	Reduced CHEOPS pain scales in the Ketamine group compared to the control group at 30 minutes and also at 6 hours after the surgery (p=0.003 AND p=0.023, respectively). NS in the mean of CHEOPS between the two groups at 12 h after the surgery.	NS between the two groups regarding the frequency of need for rescue analgesics (p=0.297)

18	Bameshki SA et al. 2015	5-12 years	N=50 Study Group, n=25 Control Group, n=25	Tonsillectomy Study Group: IV Ketamine 1 mg/kg + Midazolam *vs.* Control group: Midazolam Preoperatively	Reduced pain score at 15 and 30 minutes after extubation in the study group (p=0.007, p=0.058 respectively)	NS in the average consumption of analgesia after surgery and in the first day of admission in the two groups. Increased time to request for analgesia in the Study group, although the difference was not statistically significant (p=0.276, p=0.166).
19	Javid MJ et al. 2012	3-10 years	N=75 IV ketamine Group, n=25 SC ketamine Group, n=25 Control Group, n=25	Tonsillectomy IV ketamine Group: IV Ketamine 0.5 mg/kg *vs.* SC ketamine Group: SC Ketamine 0.5 mg/kg *vs.* Control Group: Placebo At the end of the operation	Reduced pain score at the IV or SC ketamine groups compared with the placebo group at all intervals (p<0.01). Reduced Pain score in IV ketamine group than SC ketamine after 5 min postoperatively (p<0.001). Reduced pain score after 1 and 6 hours postoperatively in SC ketamine group compared with the IV group (p=0.007 and p=0.03 respectively).	Reduced meperidine consumption in IV ketamine group (p<0.001) and SC ketamine (p<0.001) compared with the placebo group. NS in analgesic requirements between the ketamine S.C and IV groups (p=0.9).
20	Norouzi A et al. 2015	3-9 years	N=92 Oral Group, n=46 Peritonsillar Group, n=46	Tonsillectomy Oral Group: oral Ketamine 5 mg/kg *vs.* Peritonsillar Group: peritonsillar Ketamine 0.5 mg/kg Preoperatively	Reduced pain 6 hours after surgery according to CHEOPS criteria in the peritonsillar group than in the oral group (p<0.001)	----------
21	Dal D et al. 2007	2 -12 years	N=90 Group I, n=30 Group II, n=30 Group III, n=30	Tonsillectomy Group I: N/S IV *vs.* Group II: Ketamine IV 0.5mg/kg *vs.* Group III: Peritonsillar infiltration of Ketamine 0.5 mg/kg Preoperatively	Reduced pain scores in Ketamine groups compared with placebo regarding the OPS scores observed at 15, 30 and 60 min in the PACU (p<0.05). NS between Group II and Group III (p>0.05). Reduced pain in Group II and group III than group I at home (p=0.023).	Reduced rescue analgesics required (Metamizol, Acetaminophene) in Ketamine groups compared with the placebo group (p<0.001). Reduced time to reach rescue analgesia in group I (p=0.006). NS between group II and group III.
22	Yenigun A et al. 2015	5-15 years	N=120 Group 1, n=30 Group 2, n=30 Group 3, n=30 Control Group, n=30	Tonsillectomy Group 1: IV Ketamine 0.5 mg/kg *vs.* Group 2: Rectal Ketamine 0.5 mg/kg *vs.* Group 3: Peritonsillar Ketamine 2 mg/kg *vs.* Control Group: IV Tramadol Preoperatively	NS in CHEOPS scores at minutes 15, 30, and 60 as well as hours 2 and 12 between all groups. Reduced pain scores in Group 1, at 6 and 24 h compared with Group 2 and 3 (p=0.045, p=0.011). NS in pain scores between Group 1 and Control Group during first 24 h.	
Ketamine - Peritonsillar infiltration						
23	Erhan OL et al. 2007	3-7 years	N=60 Group S, n=30 Group K, n=30	Tonsillectomy Topical injection: Group S: N/S *vs.* Group K: Ketamine 0.5 mg/kg Preoperatively	Reduced CHEOPS value in Group K (p<0.05)	Reduced time of the first analgesic administration in Group K (p<0.05). Reduced total amount of analgesics in an 8-hour period in Group K (p<0.05).
24	Honarmand A et al. 2008	3-7 years	N=66 RS Group, n=33 RK Group, n=33	Tonsillectomy RS Group: Ropivacaine + N/S *vs.* RK Group: Ropivacaine + Ketamine 20 mg Preoperatively	Reduced mCHEOPS scores in the RK group at 15 min (p=0.046)	Increased analgesics until 1 h after surgery in RS group (p<0.05). Increased analgesics received during 1-24 h after surgery in RK group (p<0.05).

25	Honarmand A et al. 2008	3-12 years	N=75 Group S, n=25 Group K1, n=25 Group K2, n=25	Tonsillectomy Group S: N/S *vs.* Group K1: Ketamine 0.5 mg/kg *vs.* Group K2: Ketamine 1 mg/kg) Preoperatively	Increased CHEOPS scores in group S compared with group K1 or K2 in the first postoperative 24 h (P<0.001). NS between Group K1 and Group K2 (p>0.05).	Reduced number of patients needed analgesics in Groups K1 or K2 compared with Group S (p<0.001). Reduced time for the first analgesic requirement in Group S *vs.* Groups K1 and K2 (p<0.001). Increased total analgesic consumption in Group S (p<0.001 *vs.* Groups K1 and K2).
26	Sarafraz M et al. 2016		N=120 Ketamine Group, n=30 Tramadol Group, n=30 Lidocaine group, n=30 Control group, n=30	Tonsillectomy 1 ml injected in each tonsil: Ketamine Group: Ketamine *vs.* Tramadol Group: Tramadol *vs.* Lidocaine group: Lidocaine *vs.* Control group: N/S Intraoperatively	NS regarding pain quantity among ketamine, tramadol, lidocaine and placebo group in the first 24 h after tonsillectomy.	NS in the first time of analgesic .requirement among groups in the first 24 h after tonsillectomy.
Ketamine vs Opioids - IV administration						
27	Umuroglu T et al. 2004	5-12 years	N= 60 Group K, n=15 Group M, n=15 Group T, n=15 Group S, n=15	Tonsillectomy Group K: IV Ketamine 0.5 mg/kg *vs.* Group M: IV Morphine 0.1 mg/kg *vs.* Group T: IV Tramadol 1.5 mg/kg *vs.* Group S: IV N/S Preoperatively	Reduced pain scores (NRS, CHEOPS) in Group M at 1st, 5th, 15th, 60th min compared with Group S (p<0.05). Reduced pain scores in Group K and T at 1st and 5th min compared with Group S (p<0.05)	Increased time to the first rescue analgesic requirement (pethidine) in Group M compared with Group S (p<0.05) and Group K (p<0.01) at the first 360 min. Reduced number of patients required rescue analgesics in Group M compared with Group T (40% *vs.* 60%), Group K (40% *vs.* 73.3%) and Group S (40% *vs.* 100%).
28	Elshammaa N. et al. 2011	2-7 years	N=60 F1 group, n=15 F2 group, n=15 K group, n=15 FK group, n=15	Tonsillectomy F1 group: Fentanyl 1 mc/kg *vs.* F2 group: Fentanyl 2 mc/kg *vs.* K group: Ketamine 0.5 mg/kg *vs.* FK group: Fentanyl 2 mc/kg + Ketamine 0.5 mg/kg Preoperatively	Reduced pain scores (using the pediatric behavioral FLACC pain scale) on arrival to PACU and at 30, 60, and 90 min after arrival for K and FK compared with the F1 group (p=0.02 and p=0.0048, respectively)	NS in the need for supplemental analgesia (fentanyl)
Ketamine vs Opioids - Peritonsillar infiltration						
29	Canbay O et al. 2008	3-12 years	N= 60 Group K, n=15 Group KM, n= 15 Group M, n=15 Group C, n=15	Tonsillectomy Group K: Ketamine 20 mg *vs.* Group KM: Ketamine 20 mg + Morphine 20 mg *vs.* Group M: Morphine 20 mg *vs.* Group C: Placebo At the end of the surgery	Reduced pain at 30th, 60th,120th min and at 24th hour evaluated by the modified Hannallah scale in Groups K, M and KM compared with Group C (p<0.05). Increased pain scores in Group C at arrival to the PACU (p<0.05).	Increased effective analgesia time in Groups K, M and KM compared with Group C (p<0.05). Reduced 24 h analgesic consumption (metamizol) in Groups K, M and KM compared with Group C (p<0.05). NS in 24 h analgesic consumption between Groups K, M and KM.
30	El Sonbaty MI et al. 2011	5-15 years	N=100 Group K1, n=25 Group M1, n=25 Group K2, n=25 Group M2, n=25	Tonsillectomy Group K1: Ketamine 0.5 mg/kg *vs.* Group M1: Meperidine 1 mg/kg *vs.* Group K2: Ketamine 0.5 mg/kg + Bupivacaine *vs.* Group M2: Meperidine 1 mg/kg + Bupivacaine Preoperatively	Reduced OPS scores in Group KM at 60th and 90th min compared with Groups K1 and M1 (p<0.05)	

31	Ugur KS et al. 2013	3–10 years	N = 75 Tramadol Group, n=25 Ketamine Group, n=25 Control Group, n=25	Tonsillectomy Tramadol Group: Tramadol 2 mg/kg *vs.* Ketamine Group: Ketamine 0.5 mg/kg *vs.* Control Group: N/S Preoperatively	Reduced mCHEOPS scores at 10, 30 min, 1 hour, and 8 hours in Tramadol Group compared to Control ($p<0.05$). Reduced mCHEOPS scores at 10 min, 1 hour, 8 hours in Ketamine Group compared to Control Group ($p<0.05$). NS between Tramadol and Ketamine groups ($p>0.05$).	Reduced request of analgesia (paracetamol) in Tramadol and Ketamine groups compared to Control group ($p<0.05$) evaluated for 24 h. NS in first time for additional analgesia between all groups.
32	Tekelioglu UY et al. 2013	4 - 10 years	N= 60 Group K, n=20 Group T, n=20 Group C, n=20	Tonsillectomy Group K: Ketamine 20 mg *vs.* Group T: Tramadol 40 mg *vs.* Group C: N/S At the end of surgery	Reduced Wong-Baker FACES Pain Rating Scale Scores in all time points in Groups K and T compared with Group C ($p<0.004$). Reduced pain scores in Group T compared with Group K at 30^{th} min and 2^{nd} h ($p<0.004$). Reduced pain scores at the 40^{th} min in Group T compared to Group K ($p=0.002$) and Group K compared to Group C ($p<0.001$). Reduced pain scores in Group K compared to Group C in 5^{th}, 10^{th} min, 1^{st} h and 4 h.	Reduced rescue analgesia (meperidine) necessity in 5^{th} and 10^{th} min in Group K ($p<0.001$) and Group T ($p=0.003$) compared with Group C. NS in rescue analgesia necessity between the Group T and Group K in all time points.
OPIOIDS						
Tramadol – IV						
33	Ozköse Z et al. 2000	2 - 11 years	N=45 Group PL, n=15 Group T1, n=15 Group T2, n=15	Tonsillectomy Group PL: N/S *vs.* Group T1: Tramadol 0.5 mg/ kg *vs.* Group T2: Tramadol 1 mg/kg Preoperatively	Decreased pain scores in tramadol groups to 15^{th} and 30^{th} min after operation ($p<0.05$)	Increase number of patients needed analgesic medicine at the end of the first hour after operation in placebo group compared with the tramadol groups ($p<0.001$).
34	Cocelli LP et al. 2012	2–9 years	N=90 Group I, n=30 Group II, n=30 Group III, n=30	Tonsillectomy Group I: N/S IV *vs.* Group II: 0.75% Ropivacaine 1.5 ml to the tonsil lodge *vs.* Group III: Tramadol IV 1mg/ kg Preoperatively	Reduced Maunuksela pain scores in Group III at 2^{nd} and 24^{th} hour than in Group I ($p<0.001$). Reduced Maunuksela pain scores at 2^{nd}, 3^{rd}, 6^{th} and 9^{th} hour while resting in Group II compared with Groups I and III ($p<0.001$) NS between groups I and III. Reduced Maunuksela pain scores during swallowing in Group II compared with Group I and III at 2^{nd}, 3^{rd}, 6^{th}, 9^{th}, 12^{th}, 21^{st} and 24^{th} hour postoperatively ($p < 0.001$).	Reduced analgesic needs (paracetamol) in Group II ($p<0.05$). NS between Groups I and III.
35	Bedirli N et al. 2017	2-12 years	N=77 Group T, n=39 Group D, n=38	Tonsillectomy Group Group T: IV Tramadol 2 mg/kg *vs.* Group D: IV Dexmedetomidine 1µg/kg Preoperatively	NS in pain scores (OPS) 60 min postoperatively	NS in rescue morphine requirements

Tramadol - Topical infiltration						
36	Atef A et al. 2008	3-10 years	N= 40 Group1, n=20 Group 2, n=20	Tonsillectomy Group 1: N/S *vs.* Group@: Tramadol 2 mg/ kg Preoperatively	Reduced average recovery room admission pain score in Group 2 (p<0.05). Reduced mean pain score in group 2 24 h after surgery (p<0.05). NS between the two groups at mean pain scores from 6 h after injection and thereafter.	Increased number of patients requiring additional analgesia in the recovery room immediately after surgery in group 1 compared with group 2 (p<0.05). Increased number of doses of paracetamol in group 1 than in group 2 in order to maintain analgesia in the first 12 hours (p<0.05).
37	Ugur MB et al. 2007	7–16 years	N=45 INF group, n=15 IM group, n=15 PL group, n=15	Tonsillectomy INF group: Tramadol 2 mg/ kg to the peritonsillar area *vs.* IM group: Tramadol 2 mg/kg intramuscular *vs.* PL group: N/S Preoperatively	Reduced VAS scores on awakening in INF compared to PL group (p=0.015). NS between IM and PL groups. Increased mean VAS score for 24 h in the PL group than both groups (p<0.05).	Increased number of children required analgesics within the 1st hour after surgery in PL compared to the INF group (p=0.036)
38	Honarmand A et al. 2015	5-15 years	N=120 Group B, n=30 Group T, n=30 Group BT, n=30 Group C, n=30	Tonsillectomy Peritonsillar infiltration with: Group B: Bupivacaine 1 mg/kg *vs.* Group T: Tramadol 2 mg/kg *vs.* Group BT: Bupivacaine + Tramadol *vs.* Group C: N/S Preoperatively	Reduced pain scores in 60 minutes in the first three groups compared with Group C (p<0.05). Reduced pain scores in Group BT compared with the others in 60 min (p<0.05). Four hours after surgery, control of pain was better in the second and third groups in comparison to Groups B and Group C (p<0.05) and was better in the third group in comparison to the second group. Then, 24 hours after that, only in the group III the control of pain was effective (p<0.05).	
Dextromethorphan						
39	Rose JB et al. 1999	6–12 years	N=57 Placebo group, n=19 Dextromethorphan 0.5 group, n=19 Dextromethorphan 1.0 group, n=19	Tonsillectomy Placebo group: Placebo *vs.* Dextromethorphan 0.5 group: Dextromethorphan 0.5 mg/kg *vs.* Dextromethorphan 1.0 group: Dextromethorphan 1.0 mg/kg Preoperatively	NS at the maximal and discharge CHEOPS scores	NS with regard to the number of patients who required morphine in the PACU. NS at the mean dose of morphine in the PACU.
40	Dawson GS et al. 2001	3 - 13 years	N=40 Dextromethorphan group, n=21 Placebo group, n=19	Tonsillectomy Dextromethorphan group: Dextromethorphan Syr. 1 mg/kg *vs.* Placebo group: Placebo Preoperatively		Reduced number of patients in the dextromethorphan group required morphine compared with the placebo group (p=0 .03). Reduced mean total dose requirement of morphine in the dextromethorphan group compared to placebo (p=0 .017).
NSAIDs						
41	Kokki H. et al. 1999	1 - 12 years	N=59 KETO group, n= 30 PLACE group, n=29	Strabismus surgery KETO group: Ketoprofen 1 mg/kg preoperatively + infusion of 1 mg/kg over 2 h *vs.* PLACE group: N/S	Reduced pain at 30 min in the KETO group compared with the PLACE group (p=0.02). Reduced worst pain observed in the PACU in the KETO group compared with the PLACE group (p=0.035).	Reduced number of fentanyl doses in the PACU during the first 2-hour period in the KETO group compared with the PLACE group (p=0.047). NS at the time to the first dose of rescue analgesic between the KETO group and the PLACE group.

42	Oztekin S et al. 2002	5-14 years	N=40 Diclofenac group, n=20 Control group, n=20	Tonsillectomy Diclofenac group: Diclofenac suppository 1mg/kg preoperatively *vs.* Control group: nothing	Reduced VAS scores on arrival to the PACU, in the Diclofenac group compared with the Control group ($p<0.01$). Reduced mean VAS score in the PACU, in Diclofenac group compared with the control group ($p<0.05$).	Reduced total morphine consumption in diclofenac group than the in the control in the PACU and the ward ($p<0.012$, $p<0.021$, respectively).
OTHER DRUGS						
43	Karaaslan K et al. 2008	3-12 years	N=75 Group S, n=25 Group L, n=25 Group M, n=25	Tonsillectomy Group S: N/S *vs.* Group L: Levobupivacaine 0.25% *vs.* Group M: Levobupivacaine 0.25% + Magnesium Sulphate 2 mg/kg Given At the end of the surgery	Reduced CHEOPS values at postoperative 4th, 8th, and 16th hour in Group L&M than control group ($p<0.05$	Reduced total analgesic requirement in Group L&M at the end of postoperative 24th hour compared to Group S ($p<0.05$)
44	Mahgoobifard M et al. 2014	4 - 12 years	N=60 Group A, n=21 Group B, n=18 Group C, n=21	Tonsillectomy Group A: oral Ibuprofen 10 mg/kg *vs.* Group B: oral Acetaminophen 15 mg/kg *vs.* Group C: Placebo Given 30 minutes before the operation	Reduced average pain intensities in acetaminophen group based on the CHEOPS in both PACU and ward compared to ibuprofen or placebo groups ($p<0.002$). NS in pain intensity between the ibuprofen and placebo groups.	
45	Olutoye OA et al. 2010		N=108 Group I, n=27 Group II, n=27 Group III, n=27 Group IV, n=27	Tonsillectomy A single intraoperative dose of: Group I: Dexmedetomidine 0.75 microg/kg *vs.* Group II: Dexmedetomidine 1 microg/kg *vs.* Group III: Morphine 50 microg/kg *vs.* Group IV: Morphine 100 microg/kg Given 10 min after endotracheal intubation		Increased time to first analgesic and reduced need for additional rescue analgesia doses, in dexmedetomidine 1 microg/kg and morphine 100 microg/kg groups ($p<0.01$). NS in total postoperative rescue opioid requirements between groups.
46	Obayah GM et al. 2010		N=30 Group B, n=15 Group BD, n=15	Cleft palate repair Greater palatine nerve block with: Group B: Bupivacaine 0.25% *vs.* Group BD: Bupivacaine 0.25% + Dexmedetomidine. 1 microg/kg	Reduced pain score in the BD group as compared with the B group ($p<0.05$)	The time to the first request for analgesia was significantly longer in children in the BD group (mean 22 hours, range 20.6-23.7 h) as compared with those who received bupivacaine alone (14.2 h, 13-15 h).

RCTs: Randomized controlled trials, NR: Number of reference, N/S: Normal Saline, VAS: Visual Analogue scale, PO: Postoperative, NS: Non-significant difference, OPS: Observational Pain Scale, IV: Intravenous, mCHEOPS: modified Children's Hospital of Eastern Ontario Pain Scale, PACU: Post-Anaesthesia Care Unit, NRS: Numerical Rating Scale, NSAIDs: Non-steroidal anti-inflammatory drugs, CHEOPS: Children's Hospital of Eastern Ontario pain scale

Ontario Pain Scale (CHEOPS), the maunuksela pain scale, the FACES rating pain scale score, the Children and Infants Postoperative Pain Scale (CHIPPS), the Face, Legs, Activity, Cry, Consolability scale (FLACC scale) and All India Institute of Medical Sciences pain discomfort scale (AIIMS), so that there is uniformity of pain assessment.

Description of included patients

The age of the recruited children ranged from 1.5 months to 17 years old, their physical status according to the American Society of Anaesthesiologists (ASA) classification was limited to I or II and all received preemptive or preventive analgesia for postoperative pain management.

Interventions studied

Different analgesic techniques were performed for postoperative pain management in the context of preemptive/preventive analgesia at those studies that met our inclusion criteria. These techniques include systemic analgesia by oral, intravenous, intramuscular or rectal administration of an agent, or regional analgesia by neuraxial or local administration.

Drugs used in the concept of preemptive/preventive analgesia

in the eligible studies were acetaminophen, NSAIDs (diclofenac, ibuprofen and ketorolac), opioids (dextromethorphan, tramadol) and adjuvants (ketamine, dexmedetomidine, clonidine, neostigmine, magnesium). In studies investigating the postoperative analgesic efficacy of regional and local blocks the administered local anaesthetics were lidocaine, bupivacaine or ropivacaine.

The locoregional analgesic techniques used in order to estimate their potential preemptive efficacy were caudal blocks (with lignocaine or bupivacaine and tramadol or morphine), regional nerve blockades with bupivacaine or ropivacaine (axillary block, great auricular nerve block, intercostal nerve block) and submucous infiltration of ropivacaine.

Results and Discussion

Head and neck operations

There are a number of studies evaluating the feasibility and efficacy of preemptive/preventive analgesia in head and neck operations in children. The surgery type most performed in our selected trials is tonsillectomy as it has been documented as one of the most frequently performed surgical procedures in children and it is repeatedly identified as a procedure with a high incidence of postoperative pain. A total of 36 trials included in our analysis, evaluating the preemptive role of intravenous or peritonsillar infusion of different agents for post-tonsillectomy pain relief in children and only 1 is referred to pain control after Strabismus surgery (Table 1).

Clonidine: Only three studies met our inclusion criteria, investigating the analgesic efficacy of clonidine as part of a multimodal approach for postoperative pain management following tonsillectomy [11-13]. Two studies referred to pre-tonsillectomy peritonsillar injection came up with opposite results. Giannoni et al. [11] proved that adding clonidine to a local anaesthetic; children experienced less pain and consumed fewer analgesics. On the contrary, Moss et al. [12] ten years later failed to confirm these findings. Moreover, it is notable that rectal premedication with clonidine was associated with a significant reduction of pain in the early postoperative period compared to midazolam according to Bergendahl HT study in 2004 [13].

Ketamine: On the other hand, there are several studies referred to the preventive/preemptive analgesic effect of ketamine. Nineteen studies are included in our analysis evaluating the postoperative analgesic efficacy of ketamine in children undergoing tonsillectomy [14-32]. Four studies are referred to the efficacy of the intravenous administration of ketamine compared with placebo with positive results [14-17]. Furthermore, one study demonstrated that the addition of ketamine to midazolam preoperatively reduced postoperative pain in the first 30 min [18]. Our research revealed another 4 trials evaluating the efficacy of intravenous, subcutaneous, peritonsillar infiltration or oral administration of ketamine and showed that both subcutaneous and intravenous injections of ketamine were equal in terms of postoperative pain control and the superior efficacy of peritonsillar infiltration compared with oral administration [19-22]. Furthermore, 3 studies aimed to investigate the effectiveness of peritonsillar infiltration, showed that topical ketamine may reduce immediate postoperative pain and analgesic requirements [23-25]. That finding was not confirmed in 2016 by Sarafraz et al. [26]. In addition, a dose ranging study performed by Honarmand et al. [25], found that a dose of 0.5 mg/kg or 1 mg/kg of ketamine given 3 min before provides equally efficient pain relief during 24 h after surgery.

Moreover, 7 studies met our inclusion criteria, investigating the preemptive analgesic efficacy of ketamine compared with opioids [26-32]. In general, literature regarding the preemptive use of ketamine in children underwent tonsillectomies appeared with supportive results. The comparison between ketamine and opioids proved its effectiveness but not its superiority. Thus, ketamine may be recommended as an alternative safe option to opioids for postoperative pain relief after tonsillectomy in children, although it can be administered in combination with them, when needed. Once more, it is of note Sarafraz et al. [26] study which came up with opposite results.

Opioids: In our research, 9 trials were eligible investigating the preemptive role of opioids in children undergoing tonsillectomy [26,33-40]. The opioids used were tramadol in 7 studies and dextromethorphan in 2 studies. From the studies conducted with tramadol, one evaluates the preemptive role of intravenous administration compared with placebo and showed that tramadol in lower doses (0.5 mg/kg) was an efficient preemptive analgesic for providing analgesia in the early period [33]. On the contrary, in 2012, Cocelli et al. [34] questioned these findings. One step further, another trial designed to compare the efficacy of an intraoperative single dose of tramadol and dexmedetomidine, concluded that both tramadol and dexmedetomidine were almost equally effective for controlling pain, although it was lucking control group [35]. The rest 3 studies investigated the peritonsillar infiltration of tramadol and concluded that topical infiltration of the peritonsillar area with tramadol provided significantly better early postoperative analgesia compared with placebo, although peritonsillar bupivacaine plus tramadol infiltration had better analgesic results [36-38]. Two trials were eligible in our analysis, investigating the preemptive analgesic efficacy of dextromethorphan and came up with conflicting results [39,40].

NSAIDs: Preemptive/Preventive use of NSAIDs on postoperative pain was investigated in literature, as well [41,42]. Kokki et al. [41] investigated the preventive analgesic role of intravenous ketorolac in children undergoing Strabismus surgery, while Oztekin et al. [42] evaluated the effect of pre-incisional rectal diclofenac in children undergoing tonsillectomy. The above studies showed that preventive and preemptive use of NSAIDs can reduce early postoperative pain scores and opioids consumption.

Other drugs: In 2008, Karaaslan et al. [43] performed a trial to evaluate whether the addition of magnesium to levobupivacaine peritonsillar infiltration will decrease the postoperative analgesic requirements and concluded with supportive results. Furthermore, in 2014, Mahgoobifard et al. [44] showed that the administration of oral acetaminophen as a preemptive adjuvant may result in significantly lower pain intensity in PACU and ward, compared to ibuprofen and placebo. This beneficial effect, however, has not been proven with the preemptive administration of ibuprofen [44]. At last, our searching in literature revealed two studies investigating the postoperative analgesic effect of dexmedetomidine with very promising results [45,46]. In particular, Olutoye et al. [45] proved the beneficial effect of intraoperative dexmedetomidine on postoperative analgesia in children undergoing tonsillectomy, given intravenously. The same year, Obayah et al. [46] confirmed that the addition of dexmedetomidine to bupivacaine for greater palatine nerve block prolongs postoperative analgesia after cleft palate repair.

Table 2: RCTs assessing the preemtive/preventive analgesic efficacy of different agents in children undergoing Urological and Lower Abdominal procedures.

NR	Author/ Year	Ages	Sample size/Groups	Surgery/ Protocol/ Time of drug administration	Postoperative pain intensity	Analgesic Consumption
KETAMINE						
Ketamine IV						
47	Becke K et al. 2005	1–12 years	N=30 Ketamine group, n=15 Control group, n=15	Major urological surgery Ketamine group: an IV preoperative bolus of ketamine 0.2 mg/kg followed by a continuous infusion of 5 μg/kg/min *vs.* Control group: N/S	Reduced pain scores during the first PO hour (p<0.05)	NS in morphine consumption during the first 72 hours. Increased time to first morphine administration in the Ketamine group (p<0.01). Increased time to first PCA request in the Ketamine group (p<0.05).
48	Talu GK et al. 2008	1-12 years	N= 60 Group K, n=20 Group R, n=20 Group RK, n=20	Elective hernia repair Group K: ketamine IV 0.5 mg/kg *vs.* Group R: Ropivacaine caudally + N/S IV *vs.* Group RK: Ropivacaine caudally + ketamine IV 0.5 mg/kg Preoperatively	Increased pain scores at the 10 & 30 min, & 2nd h, 4th h and 8th h in Group K compared with Group R and Group RK (p<0.001)	Increased analgesic consumption (acetaminophen) in Group K compared with groups R and RK (p<0.05). NS in acetaminophen consumption between groups R and RK. Reduced time to first analgesic use in Group K compared with group R and Group RK (p<0.05).
Ketamine IV vs Caudally						
49	Martindale SJ et al. 2004	3 months - 6 years	N=60 Bupivacaine Group, n=20 Caudal ketamine group, n=20 I.V. ketamine Group, n=20	Sub-umbilical surgery Bupivicaine group: bupivacaine *vs.* Caudal ketamine group: bupivacaine + caudal ketamine 0.5 mg/kg *vs.* IV ketamine group: bupivacaine + ketamine IV 0.5 mg/kg Preoperatively	NS in pain scores at 1st, 2nd, 4th, 24th h	Increased median time to first analgesia (paracetamol) in the caudal ketamine group than in the IV ketamine or bupivacaine groups (p=0.01). Reduced doses of analgesia over the first 24 h in the caudal ketamine group compared with the IV ketamine or bupivacaine groups (p<0.05). NS between the IV ketamine and bupivacaine groups.
Ketamine Caudally						
50	Panjabi N et al. 2004	6 months - 10 years	N=60 Group 1, n=20 Group 2, n=20 Group 3, n=20	Inguinal herniotomy Group 1: bupivacaine + ketamine 0.25 mg/kg *vs.* Group 2: bupivacaine + ketamine 0.5 mg/kg *vs.* Group 3: bupivacaine + ketamine 1 mg/kg Preoperatively		Reduced duration of analgesia (time to first analgesic) in group 1 than in the other 2 groups (p<0.01). NS in the duration of analgesia between groups 2 and 3. Increased number of patients requiring supplemental analgesia (pethidine) in group 1 compared with group 2 and group 3 during the first 24 h (p<0.001).
51	Gunes Y et al. 2004	1 -10 years	N= 99 Group R, n=32 Group RK, n=33 Group RT, n=34	Elective inguinal hernia repair Group R: ropivacaine *vs.* Group RK: ropivacaine + Ketamine 0.25 mg/kg *vs.* Group RT: ropivacaine + Tramadol 1 mg/kg Preoperatively	Reduced pain scores in group RK than group R at 3h (p=0.049). Reduced pain scores in group RT than group R at 3 hours (p=0.003).	Increased duration of analgesia in group RT than group R (p=0.001). Reduced number of patients in Group RT required supplementary analgesics (paracetamol) in the first 24 hours compared with group R and group RK (p=0.005).
52	Gunduz M et al. 2006	1 - 10 years	N=62 Group KL, n=32 Group KT, n=30	Hypospadias surgery Group KL: ketamine 0.25 mg/kg + lidocaine *vs.* Group KT: ketamine 0.25 mg/kg + Tramadol 1 mg/kg Preoperatively	Reduced pain scores in group KL than in group KT at first 3 h (p<0.007) except at first 15 min	NS at duration of analgesia. NS at supplementary doses needed (paracetamol) during the 24 h study period.

53	Odes R et al. 2010	1-4 years	N=45 Group R, n=15 Group K, n=15 Group R+K, n=15	Inguinal hernia repair Group R: Ropivacaine *vs.* Group K: Ketamine 0.5 mg/kg *vs.* Group R+K : Ropivacaine + Ketamine 0.5 mg/kg Preoperatively	NS in pain scores in intra-group analysis. Increased pain scores 45 min in Group R compared to Group K and Group R+K (p<0.05). Increased pain scores in Group R compared to Group R+K at 60 min (p<0.05).	Increased effective analgesic period in Group K and Group R+K than in Group R (p<0.05). Reduced number of patients who required analgesics in the first 24 hours in Group R+K than the other groups (p<0.05).
54	Singh J et al. 2012	1-10 years	N=80 Group B, n=20 Group BC, n=20 Group BK, n=20 Group BF, n=20	Sub-umbilical surgery Group B: bupivacaine + N/S *vs.* Group BC: bupivacaine + Clonidine 1 µg/kg *vs.* Group BK: bupivacaine + ketamine 0.5 mg/kg *vs.* Group BF: bupivacaine + fentanyl 1 mcg/kg Preoperatively	Reduced pain scores in 24 hours in Group BC compared with the other groups (p<0.05)	Increased mean duration of analgesia in Group BC than in Group BK, Group BF and Group B (p<0.05). Reduced requirements of rescue medicine in Group BC (p<0.05).
CLONIDINE						
Clonidine Caudal						
55	Wheeler M et al. 2005	2–8 years	N=30 Group C, n=15 Group NC, n=15	Sub-umbilical surgery Group-C: bupivacaine + clonidine 2 µg/ kg *vs.* Group-NC: bupivacaine Preoperatively	NS in pain scores collected in the immediate PO period	NS in time to first analgesic rescue (morphine or oral analgesic). NS in the number of patients requiring rescue analgesic medication at 4, 6, 8, 12, and 24 h.
56	Fernandes ML et al. 2012	1–10 years	N=80 Group B, n=20 Group BM, n=20 Group BC, n=20 Group BMC, n=20	Infra-umbilical urological and genital procedures Group B: bupivacaine *vs.* Group BM: bupivacaine + Morphine 20 µg/kg *vs.* Group BC: bupivacaine + Clonidine 1µg/kg *vs.* Group BMC: bupivacaine + Morphine 20 µg/kg+ Clonidine 1 µg/kg Preoperatively	Reduced pain scores at 6, 12, and 24 hours after surgery at Groups BM and BMC (p<0.05)	Reduced number of patients requiring analgesics during the first 24 hours in Groups BM and BMC compared with Groups B and BC (p<0.05). Reduced number of rescue doses of metamizol in the groups with morphine during the first 24 h (p=0.002). NS regarding the number of doses of ibuprofen and morphine. NS at the time to first rescue analgesia.
57	Akin A et al. 2010	2–8 years	N=60 Group L, n=20 Group L-Ccau, n= 20 Group L-Civ, n=20	Inguinal hernia repair/orchidopexy surgery Group L: caudal levobupivacaine + IV N/S *vs.* Group L-Ccau: caudal levobupivacaine + Clonidine 2 µg/ kg + IV N/S *vs.* Group L-Civ : caudal levobupivacaine + IV Clonidine 2 µg/kg Preoperatively	Reduced pain scores in the first 24 h in groups Group L-Ccau and Group L-Civ (p<0.05)	Increased median time to first analgesic demand in Group L-Ccau compared to Group L and Group L-Civ (p<0.05). Reduced number of patients in Group L-Ccau who required rescue analgesia (tramadol) in the first 24 h postoperatively compared to Group L and Group L-Civ (p<0.05).
58	Sanwatsarkar S et al. 2017	1-7 years	N=75 Group B, n=25 Group BC, n=25 Group BM, n=25	Infra-umbilical surgeries Group B: caudal bupivacaine *vs.* Group BC: bupivacaine + Clonidine 1 µg/kg *vs.* Group BM: bupivacaine + midazolam 30 µg/kg Preoperatively	Increased duration of analgesia in Groups BC, BM compared to Group B (p=0.001). Increased FLACC pain score in Group B at the end of 4th, 8th and 12th hour compared with Group BC and Group BM. Increased pain scores at the end of 12th h, in Group BM compared to Group BC.	Reduced number of analgesics required in Group BC compared with Group BM and Group B (p<0.01)

Clonidine Peripheral nerve block						
59	Kaabachi O et al. 2005	1-12 years	N= 98 Group C, n=49 Group P, n=49	Elective herniorrhaphy or orchidopexy Group C: bupivacaine + Clonidine 1 μg/kg *vs.* Group P: only bupivacaine Preoperatively	NS in number of patients free from pain during the early and late PO period. NS at parental satisfaction with postoperative pain relief.	NS in the rate of rescue analgesia during the first six postoperative hours. NS at the time for the first analgesic request during hospital stay. NS at the number of patients receiving analgesic rescue during the 24-h study period (Paracetamol).
NEOSTIGMINE						
60	Turan A et al. 2003	1–6 years	N= 44 Group I, n=22 Group II, n=22	Elective surgery of inguinal hernia or hypospadias Group I: ropivacaine caudally *vs.* Group II: ropivacaine + neostigmine 2 μg/kg caudally Preoperatively	Reduced pain scores in Group II at 6 and 12 h compared with Group I ($p<0.05$)	Increased time to first analgesic requirement (rectal paracetamol) in Group II compared with Group I ($p<0.05$). Increased total analgesic consumption at 24 h in Group I compared with Group II ($p<0.05$). Increased number of patients given paracetamol in Group I compared with Group II ($p<0.05$).
61	Mahajan R et al. 2004	Boys 2-8 years	N= 80 Group I, n=20 Group II, n=20 Group III, n=20 Group IV, n=20	Surgical repair of hypospadias Group I: bupivacaine *vs.* Group II: bupivacaine +neostigmine 2 μg/kg *vs.* Group III: bupivacaine + neostigmine 3 μg/kg *vs.* Group IV: bupivacaine + neostigmine 4 μg/kg Preoperatively		Reduced duration of PO analgesia = Mean time to first administration of rescue analgesia in Group I compared with Group II, Group III and Group IV ($p<0.05$). NS among Groups II, III and IV. Increased total analgesic (paracetamol) consumption (at 24 h) in Group I than in the groups II –III and IV ($p<0.05$). NS between Groups II, III and IV.
62	Karaaslan K et al. 2009	5 months - 5 years	N=60 Group I, n=20 Groups II, n=20 Groups III, n=20	Genito-urinary surgery Group I: levobupivacaine *vs.* Groups II: levobupivacaine + neostigmine 2 μg/kg *vs.* Group III: levobupivacaine + neostigmine 4 μg/kg Postoperatively	Increased pain scores in Group I at 15th minute, 1st, 2nd, 3rd, 4th, 8th, 16th and 24th h compared with the other groups ($p<0.05$)	Increased total analgesic consumption in Group I compared to neostigmine groups ($p<0.05$). NS in duration of postoperative analgesia and total analgesic consumption between Groups II and III.
OPIOIDS						
63	Ozcengiz D et al. 2001	4-10 years	N=116 Group T, n=38 Group M, n=40 Group C, n=38	Inguinal herniorrhaphy Group T: preemptive caudal Tramadol 2 mg/kg *vs.* Group M: preemptive caudal Morphine 0.03 mg/kg *vs.* Group C: Morphine 0.03 mg/kg Postoperatively	NS between groups at pain scores	NS at supplementary doses needed

RCTs: Randomized controlled trials; NR: Number of reference; NS: Non-significant difference; IV: Intravenous; PO: Postoperative; PCA: Patient Control Analgesia; N/S: Normal Saline

Urological–lower abdominal operations

The field of postsurgical children's pain relief has grown considerably over the past years, as it has been associated with chronic pain. Urological and lower abdominal operations such as inguinal hernia repair, hypospadias surgery or orchidopexy are some of the most frequently sub-umbilical surgeries performed in children. Our research investigated 29 trials evaluating the analgesic impact of preemptive/preventive analgesia on postoperative pain in urological and lower abdominal surgeries, performed in children.

Ketamine: Eight trials are referred to the potential postoperative analgesic effect of Ketamine [47-54]. Two of those was referred to the intraoperative analgesic effect of intravenous ketamine in children

Table 3: RCTs investigating the preemptive/preventive analgesic role of Dexmedetomidine in children undergoing Urological and Lower Abdominal procedures.

NR	Author/ Year	Ages	Sample size/ Groups	Surgery/ Protocol/ Time of drug administration	Postoperative pain intensity	Analgesic consumption
Dexmedetomidine - Caudal						
65	Yao Y et al. 2018	2-5 years	N=90 L-Dcau group, n=30 L-Div group, n=30 L group, n=30	Inguinal hernia repair L-Dcau group: caudal levobupivacaine + dexmedetomidine 1 μg/kg + IV N/S *vs.* L-Div group: levobupivacaine + IV dexmedetomidine 1 μg/kg +IV N/S *vs.* L group: levobupivacaine + IV N/S Preoperatively	Increased median duration of analgesia in the L-Dcau group compared to the L group ($p<0.001$) Increased median duration of analgesia in the L-Div group compared to the L group ($p<0.001$) NS between the L-Dcau and L-Div groups	Reduced number of patients required rescue analgesia in the first 24 hour, in the L-Dcau and L-Div groups compared to the L group ($p<0.05$). NS between the L-Dcau and L-Div groups.
66	Jarineshin H et al. 2016	1-5 years	N=61 Group B, n=20 Group BD, n=20 Group BF, n=21	Elective inguinal hernia repair Group B: caudal bupivacaine *vs.* Group BD: bupivacaine+ dexmedetomidine 2 μg/kg *vs.* Group BF: bupivacaine+ fentanyl 2 μg/kg Preoperatively	Reduced mean pain scores in the BD group at 30 and 60 minutes, 1st, 2nd, 4th, 6th, 12th and 24th h after the operation ($p<0.001$). Reduced mean pain scores in the BD group in the 1st, 2nd and 4th h after the operation, compared with BF group ($p<0.001$).	
67	Al-Zaben KR et al. 2016	1 -6 years	N=75 Group B, n=25 Group B-Dcau, n=25 Group B-DIV, n=25	Lower abdominal and perineal surgeries Group B: caudal bupivacaine + IV N/S *vs.* Group B-Dcau: caudal bupivacaine+ Dexmedetomidine 1 μg/kg + IV N/S *vs.* Group B-DIV: IV Dexmedetomidine 1 μg/kg in N/S Preoperatively	Reduced pain scores in Groups B-Dcau and B-DIV compared with Group B ($p<0.05$)	Increased time to first rescue analgesia in Group B-Dcau compared with groups B-DIV and B ($p<0.05$). Reduced number of patients in group B-Dcau required rescue analgesia during the first PO 24 h compared to group B and group B-DIV ($p<0.05$).
68	Goyal V et al. 2016	2-10 years	N=100 Group A, n= 50 Group B, n= 50	Infraumbilical surgeries Group A: caudal Bupivacaine + N/S *vs.* Group B: Bupivacaine + Dexmedetomidine 1 μg/kg Preoperatively	Increased mean duration of PO caudal analgesia in Group B($p<0.0001$). Reduced mean FLACC pain score in Group B throughout the initial 12 PO hours ($p<0.0001$).	Increased time of first PO rescue analgesic required in Group B ($p<0.0001$). Reduced number of rescue analgesics in Group B compared to Group A.
69	Cho JE et al. 2015	1- 6 years	N= 80 Control group, n=40 DEX group, n=40	Ambulatory Orchiopexy Control group : caudal ropivacaine + N/S *vs.* DEX group: caudal ropivacaine + Dexmedetomidine 1 μg/kg Preoperatively	Reduced FLACC pain score in the DEX group than in the control group at 30 min of PACU ($p<0.05$)	Increased time to the first analgesic request in the DEX group compared with the Control group ($p<0.05$) NS in the frequency of analgesic requirement
70	Al-Zaben KR et al. 2015	1- 6 years	N= 91 Group B, n=30 Group BD1, n=30 Group BD2, n=30	Infra-umbilical surgery Group B: bupivacaine *vs.* Group BD1: bupivacaine + Dexmedetomidine 1 μg/kg *vs.* Group BD2: bupivacaine + Dexmedetomidine 2 μg/kg Preoperatively	Reduced pain scores in Groups BD1 and BD2	Increased Time to first analgesia requirement in BD1 and BD2 groups compared to B group ($p<0.001$). Increased paracetamol analgesic requirements over 24 h in group B compared to BD1 and BD2 groups ($p<0.001$)

71	Bharti N et al. 2014	1- 8 years	N=80 Group 1, n=20 Group 2, n=20 Group 3, n=20 Group 4, n=20	Lower abdominal and perineal surgeries Group 1: caudal ropivacaine *vs.* Group 2: caudal ropivacaine + Dexmedetomidine 0.5 μg/kg *vs.* Group 3: ropivacaine + Dexmedetomidine 1.0 μg/kg *vs.* Group 4: ropivacaine + Dexmedetomidine 1.5 μg/kg Preoperatively		Prolonged postoperative analgesia in all dexmedetomidine groups compared to plain ropivacaine group (p<0.001). All patients in the plain ropivacaine group required rescue analgesia within first 6 PO hours, while none in the other three groups.
72	Anand VG et al. 2011	6 months - 6 years	N=60 Group RD, n=30 Group R, n=30	Lower abdominal surgeries Group RD: ropivacaine + Dexmedetomidine 2 μg/kg *vs.* Group R: ropivacaine + N/S Preoperatively	Reduced pain scores in Group RD compared with Group R measured 4th hourly in the postoperative period (p<0.001)	Increased mean duration of PO analgesia in Group RD compared with Group R (p<0.001)
73	El-Hennawy AM et al. 2009	6 months - 6 years	N= 60 Group A, n=20 Group B, n=20 Group C, n=20	Lower abdominal surgeries Group A: bupivacaine + dexmedetomidine 2 μg/kg *vs.* Group B: bupivacaine + clonidine 2 μg/kg *vs.* Group C: bupivacaine + N/S Preoperatively	Increased pain score measured 4 hours after discharge from the PACU in Group C compared with Groups A and B (p<0.001)	Reduced postoperative analgesia time in Group C compared with Groups A and B (p<0.001). NS between dexmedetomidine and clonidine as regards the analgesia time (p=0.796).
74	Saadawy I et al. 2009	1–6 years	N=60 Group B, n=30 Group BD, n=30	Inguinal hernia repair/ orchidopexy Group B: bupivacaine caudally *vs.* Group BD: bupivacaine + Dexmedetomidine 1 mg/kg Preoperatively	Increased duration of analgesia in Group BD (p=0.001). Reduced pain scores in Group BD (p<0.01).	Reduced total consumption of rescue analgesic in Group BD compared with Group B (p<0.01) during the 24-h PO study period
Dexmedetomidine - ilioinguinal/iliohypogastric nerve block (IINB)						
75	Lundblad M et al. 2015	1.5-8 years	N=43 Group LA, n=21 Group LAD, n=22	Inguinal hernia repair Group LA: ropivacaine *vs.* Group LAD: ropivacaine + Dexmedetomidine 0.3 μg/kg Preoperatively	Reduced number of patients with a CHIPPS score ≥ 4 in the PACU, in Group LAD (p=0.0029)	Increased median time to first PO administration of supplemental analgesia in Group LAD (p=0.0717)
Dexmedetomidine – IV						
76	Al-Zaben KR et al. 2010	1-12 years	N=48 Group P, n=24 Group D, n=24	Hypospadius surgery Group P: N/S *vs.* Group D: preoperative loading dose of IV dexmedetomidine 1 μg/kg + perioperative continuous infusion of 0.7 μg/kg/h	Reduced pain scores in Group D compared with Group P in PACU (p<0.001)	Reduced analgesic consumption (paracetamol) in Group D than group P in the ward over 24 hours (p<0.001)

RCTs: Randomized Controlled Trials; NR: Number of Reference; IV: Intravenous; N/S: Normal Saline; NS: Non-significant difference; PO: Postoperative; PACU: Post-Anaesthesia Care Unit; CHIPPS: Children and Infants Postoperative Pain Scale; FLACC scale: Face, Legs, Activity, Cry, Consolability scale

scheduled for major urological surgeries and these studies failed to prove a true 'prevention' of pain when ketamine is administered intravenously [47,48]. One study compared the analgesic efficacy of ketamine after caudal or intravenous administration and proved that ketamine's principal site of action is caudally rather than intravenously in terms of postoperative analgesic use [49]. Furthermore, Panjabi et al. [50] conducted a dose ranging study to identify the optimal dose of caudally administered ketamine and concluded that the dose of 0.5 mg/kg added to 0.75 mL/kg bupivacaine 0.25% can produce the maximum duration of caudal analgesia with minimal adverse effects. All the rest studies investigate the effectiveness of ketamine administered caudally [51-53]. These studies concluded that ketamine combined with a local anaesthetic lengthens the duration of analgesia and decreases postoperative analgesic requirements. One step further, in 2012, Singh et al. [54] performed a comparison of ketamine, fentanyl and clonidine as an adjuvant during bupivacaine caudal anaesthesia and showed the superior effectiveness of caudal clonidine in postoperative pain management in terms of pain intensity, duration of analgesia as well as requirement of rescue medicine.

Clonidine: Clonidine is an imidazoline-derivative; centrally-acting α-2 adrenergic agonist and one of the most commonly used adjuvant for preemptive analgesia. Our research revealed 6 relevant studies [54-59]. Five of them were referred to caudal administration and only one to peripheral nerve block, which failed to demonstrate any advantage in addition of clonidine to bupivacaine regarding postoperative analgesia in children [59]. Moreover, Akin et al.

[57] in 2010 made a comparison between caudal and intravenous administration and showed the superiority of caudal clonidine on postoperative pain control. In addition, Sanwatsarkar et al. [58] in 2017 compared clonidine with midazolam and found that the use of clonidine as an additive to bupivacaine in caudal epidural is a superior choice to midazolam regarding postoperative analgesic needs. In general, literature findings are supporting regarding the use of caudal administration of clonidine as an adjuvant for preemptive analgesia in the paediatric population. In particular, only one study failed to find any advantage from adding clonidine preoperatively (Wheeler et al. [55]) but it is of note its small sample size. On the other hand, the rest 4 studies strengthen clonidine's use, especially in combination with morphine [54-58].

Neostigmine: The parasympathomimetic agent neostigmine has been investigated for use as an adjunct analgesic agent in 3 studies [60-62]. The analgesic advantages of adding neostigmine to caudal anaesthesia with ropivacaine/bupivacaine was confirmed in all the above studies. Neostigmine can extend the duration of analgesia; minimize total analgesic consumption and severity of pain experience, according to their findings. In addition, research demonstrated a dose-independent analgesic effect of caudal neostigmine [61,62].

Opioids: Just one study was referred to opioids performed by Ozcengiz et al. [63] making a comparison between preemptive caudal morphine and tramadol and found no differences in the quality and duration of postoperative pain relief.

Characteristics of the above mentioned studies on ketamine, clonidine, neostigmine and opioids are summarized in Table 2.

Dexmedetomidine: Dexmedetomidine is a highly selective α2-adrenoceptor agonist that seems to be a promising adjunct to refine postoperative analgesia. A recent review article by Trifa et al. [64] on the adjunctive analgesia of dexmedetomidine in children recommends the addition of caudal dexmedetomidine to a local anaesthetic agent in patients undergoing infra-umbilical surgical procedures.

According to our research, 11 trials compared the preemptive efficacy of adding dexmedetomidine to a local anaesthetic agent [65-75]. One study investigated the preventative effect of intravenous administration [76] (Table 3). The identified studies confirmed Trifa et al. [64] findings and support the beneficial effects of dexmedetomidine during caudal anaesthesia on postoperative pain control in the paediatric population. In particular, all our eligible studies came up with supportive results. Moreover, the comparison between caudal dexmedetomidine/clonidine showed no significant advantage of dexmedetomidine over clonidine regarding analgesia duration [73]. Furthermore, 2 studies appeared to be dose-response studies and showed that doses of 0.5 μg/kg to 2 μg/kg of caudal dexmedetomidine achieved comparable prolongation of postoperative analgesia [70,71]. In addition, according to the recently published recommendations on "Local Anesthetics and Adjuvants Dosage in Pediatric Regional Anesthesia", dexmedetomidine can be used as an adjunct to prolong the duration of peripheral nerve blocks in children [77]. One study investigated the use of dexmedetomidine as an adjunct to an ilioinguinal/iliohypogastric nerve block with positive results. The use of dexmedetomidine was associated with a prolongation of the period to first supplemental analgesia demand [75]. Compared to caudal, intravenous administration of dexmedetomidine appeared less effective in one study [67]. In contrast, Yao et al. [65] recently failed to prove the greater role of neuraxial compared to that of peripheral α-2 adrenoceptors in pain processing. Moreover, Al-Zaben et al. [76] in 2010 proved the effectiveness of dexmedetomidine administered intravenously, on reducing postoperative analgesic consumption. This may suggest a debate and further investigation should be done in order to reach a safe conclusion, as regard as the route of dexmedetomidine administration.

Orthopaedics

Major orthopaedic surgeries are characterized by the need of profound postoperative analgesia, especially when they are performed in the young population. In these cases postoperative pain control is a true challenge for the anaesthesiologist. Thus, many agents have been studied for their potential preemptive effect in order to lessen postoperative pain, although only 5 studies investigating the preventative analgesic role of ketamine were eligible for our research [78-82] (Table 4).

Ketamine has been studied in a variety of clinical scenarios using different routes and dosage regimens. Especially, the scenario of a perioperative loading dose followed by continuous infusion postoperatively was studied in 4 studies [78-81]. All these studies failed to support the use of this preventive regiment in terms of postoperative pain intensity. On the other hand, one study resulted that the cumulative morphine consumption for 48 h, was reduced in children who received ketamine [79]. Additionally, 1 study compared intravenous with caudal administration and showed that caudal injection of ketamine may be superior as regard as mean time to first analgesia request and postoperative analgesic consumption [82].

Pre-incision *vs.* post-incision locoregional analgesia

Our review is also aimed to investigate the importance of the timing that the analgesic intervention was performed in relation to surgical wound incision. In this regard, pRCTs investigated the preemptive effect of locoregional analgesic techniques in different paediatric surgical settings were identified (Table 5).

Regarding orthopaedic surgery, only one study included in our review, that investigated the preemptive role of regional blockade and its results failed to indicate the superiority of preemptive analgesia in terms of pain scores improvement or analgesic requirements [83]. Three studies analyzed the preemptive ability of a regional block in urological and lower abdominal surgeries and according to their conflicting results, it is hazardous to speculate conclusions regarding the preemptive efficacy of a regional block in children undergoing urological and lower abdominal procedures [63,84,85].

Furthermore, our analysis involved 2 more studies enquiring the preemptive effectiveness of regional blocks on postoperative pain relief after head and neck surgeries and their controversial findings do not allow reaching safe conclusions, as well [86,87]. Moreover, one study investigated the effectiveness of preoperative submucous infiltration of local anaesthetic in infants and small children undergoing elective cleft palate repair with positive results [88]. Finally, one study enrolled 241 patients undergoing paediatric day surgery proved that postoperative pain intensity can be reduced by rectally administered paracetamol or diclofenac combined with regional nerve block with bupivacaine performed before surgery [89]. Although the particular study does not measure analgesic requirements, its findings are very important especially considering its big sample size.

In summary, despite some evidence suggesting beneficial effects of preemptive analgesia with regional and local blockade, evidence

Table 4: RCTs assessing the preemptive/preventive analgesic role of Ketamine in children undergoing Orthopaedic surgeries.

NR	Author/ Year	Ages	Sample size/Groups	Surgery/ Protocol	Postoperative pain intensity	Analgesic consumption
78	Perelló M et al. 2017	10-18 years	N=48 Ketamine group, n=24 Placebo group: n=24	Surgical posterior vertebral fusion Ketamine group: 0.5 mg/ kg ketamine perioperative + continuous intravenous infusion of 2 mg/kg/min until 72 h *vs.* Placebo group: placebo for 72 h	NS in pain at rest and during movement	NS in total cumulative morphine consumption for 72 h
79	Minoshima R et al. 2015	10-19 years	N=36 Ketamine group, n=17 Placebo group, n=19	Scoliosis surgery Ketamine group: ketamine infusion 2 μg/kg/min for 48 h *vs.* Placebo group: N/S	NS in pain scores	Reduced cumulative morphine consumption for 48 h after surgery in the ketamine group compared to the placebo group (p=0.019)
80	Pestieau SR. 2014	10-18 years	N=50 Ketamine group, n=29 Placebo group, n=21	Scoliosis surgery Ketamine group: Loading dose of 0.5 mg/kg preoperatively +an intraoperative infusion at 0.25 mg/kg/h + a postoperative infusion at 0.1 mg/kg/h *vs.* Placebo group: placebo	NS in pain scores	NS in morphine consumption from day 1–4
81	Engelhardt T et al. 2008	12-18 years	N=34 Ketamine group, n=16 Placebo group, n=18	Scoliosis surgery Ketamine group: ketamine at a loading dose of 0.5 mg/kg preoperatively + perioperative continuous infusion of 4 μg/kg/ min *vs.* Placebo group: placebo	NS in pain scores	NS in cumulative morphine consumption in the initial 36 h. NS in mean cumulative PCA morphine consumption at 24, 48, and 72 h.
82	Amiri HR et al. 2012	18 months-10 years	N=36 Caudal group, n=18 Intravascular group, n=18	Salter innominate osteotomy Caudal group: caudal ketamine 1 mg/kg *vs.* Intravascular group: IV ketamine 1 mg/kg Preoperatively	NS in pain scores	Increased mean time to first analgesia in the caudal ketamine group than in the intravenous ketamine group (p<0.01). Reduced number of children asked for additional analgesic drugs in the caudal group than in the intravenous group (p= 0.01) during the 24-h observation time.

RCTs: Randomized Controlled Trials; NR: Number of Reference; N/S: Normal Saline; NS: Non-significant Difference; PCA: Patient Controlled Analgesia; IV: Intravenous

based conclusions cannot be extracted. So far, literature regarding the impact of preemptive analgesia in children undergoing surgical procedures under locoregional blockade techniques is not definite and further investigation should be done.

Conclusion

Head and neck operations

All prospective trials that investigated the intravenous administration of ketamine compared with placebo came up with supportive results and proved the superior analgesic effect of preemptive intravenous ketamine for the management of postsurgical pain in children underwent tonsillectomy, maybe due to prevention of establishment of central sensitization caused by the incision. Similarly, the majority of studies analyzing the effectiveness of topical injection of ketamine concluded with almost identical results. Summarizing, as it appeared from our research, the administration of ketamine (intravenous or peritonsillar infiltration) before surgical incision in children undergoing tonsillectomy, probably can enhance postoperative analgesia quality and reduce analgesic demands. Ketamine may be recommended as an alternative safe option to opioids according to our analysis. Moreover, the preemptive and preventive role of opioids (Tramadol) is also supported in head and neck operations. Furthermore, findings are very promising regarding preoperative intravenous administration of dexmedetomidine in head and neck operations.

Orthopaedic surgical procedures

The preventative effectiveness of ketamine in orthopaedics is of question. Despite the supportive findings from several studies performed in other paediatric surgical settings, preventive administration of ketamine has not been shown to be beneficial in the management of acute postoperative pain after orthopaedic surgical procedures. Preemptive regional blockade also, has not been proven to affect postoperative pain control in children undergoing orthopaedic surgery.

Urological and lower abdominal procedures

As regard as urological procedures, caudal or intravenous ketamine seems to be effective as it lengthens the duration of analgesia and decreases postoperative analgesic requirements. A number of clinical trials provide evidence that the preoperative use of subanaesthetic doses of ketamine is associated with suppression of opioid-induced acute tolerance and injury-induced central sensitization by blockade the NMDA receptors. Moreover, adding neostigmine or clonidine to caudal anaesthesia for urological procedures seems to be an effective choice for postsurgical children's pain relief. Also, preoperative caudal administration of a single dose of dexmedetomidine can enhance postoperative pain control in children undergoing urological and lower abdominal surgeries.

The current scientific increasing interest on dexmedetomidine analgesic properties has been strongly justified according to the

Table 5: RCTs comparing the postoperative analgesic effect of pre-incision *vs.* post-incision locoregional analgesia performed in children undergoing different types of surgeries.

NR	Author/ Year	Ages	Sample size/ Groups	Surgery/ Protocol	Postoperative pain intensity	Analgesic consumption
83	Altintas F et al. 2000	1–11 years	N =49 Presurgical group, n=25 Postsurgical group, n=24	Hand and forearm surgery Presurgical Group: axillary block with 2 mg/kg of 0.25% bupivacaine before surgery *vs.* Postsurgical group: axillary block with 2mg/kg of 0.25% bupivacaine after surgery	NS in FPS scores during the first 8 h in the PO period. Increased FPS scores at 10th hour in the Presurgical Group (p<0.05). NS in FPS at 24 h after operation. Increased cumulative FPS scores in the Presurgical Group (p<0.05).	NS in cumulative analgesic requirements. Increased individual analgesic requirements for acetaminophen within the first postoperative 24 h, in the Presurgical Group (p<0.05). Increased number of patients required additional analgesic medication within the first 24 h, in the Presurgical Group (p<0.05).
84	Holthusen H et al. 1994	2.6-9.8 years	N= 25 Study Group, n=14 Control Group, n=11	Circumcision Study Group: preoperative caudal block with 0.5 ml/kg lignocaine 1% *vs.* Control Group: caudal block with 0.5 ml/kg lignocaine 1% after surgery	Increased cumulative pain score (CHEOPS), assessed every 30 min for the first 8 h after operation in the Study Group (only when the reference point was defined as the end of surgery) (p=0.04).	NS in individual or cumulative analgesic requirements for paracetamol between the two groups within the first 48 h after operation. NS in time to first analgesic administration.
85	Kundra P et al. 1998	9 months – 12 years	N = 60 Group I, n=30 Group II, n=30	Herniorraphy Group I (preemtive): 0.66 ml/kg bupivacaine 0.25% + morphine 0.02 mg/kg, caudally *vs.* Group II (postincisional group): 0.66 ml/kg bupivacaine 0.25% + morphine 0.02 mg/kg, caudally	Reduced OPS scores at all time intervals in Group I compared with Group II, during the first 24 hours (p<0.05)	Increased time to first analgesia in Group I (p<0.05). Reduced total consumption of morphine during 24-h period, in Group I (p<0.05). NS in the number of demands for rescue analgesia with morphine.
63	Ozcengiz D et al. 2001	4-10 years	N= 116 Group T, n=38 Group M, n=40 Group C, n=38	Herniorrhaphy Groyp T: Preemptive caudal block with Tramadol 2 mg/kg *vs.* Group M: Preemtive caudal block with Morphine 0.03 mg/kg *vs.* Group C: postincisional caudal block with Morphine 0.03 mg/kg	NS in OPS scores	NS in morphine consumption in a 24-h period
86	Suresh S et al. 2004	2-18 years	N= 40 Group BB, n=20 Group SB-B, n=20	Tympanomastoid Surgery Group BB: GAN -block with 2 mL of bupivacaine 0.25% before surgical incision + a second GAN-block with the same dose 1 hour before the end of surgery *vs.* Group SB-B : preoperative GAN-block with saline followed by a second GAN-block 1 h before the end of the procedure with 2 mL of bupivacaine 0.25%	NS in the OPS in the PACU or in the short-stay unit (360 min)	NS in morphine consumption in PACU
87	Coban YK et al. 2008	9 months - 5 years	N= 20 Study group, n=10 Control group, n=10	Elective Cleft Palate Repair Study group: submucous infiltration of Ropivacaine 0.2 mg/kg *vs.* Control group: no medication Preoperatively	Reduced CHIPPS in the Study Group during 48 h (p<0.05), except the scores of 4th and 48th h	Reduced number of patients required Morphine in the Study Group (2 *vs.* 6). Reduced median time to first analgesic demand in the Study Group (420 *vs.* 450 min).

88	Woo KJ et al. 2016	<18 years	N=66 Study group, n=33 Control group, n=33	Rib cartilage harvest for auricular reconstruction Study group: preventive ICNB with 0.5% bupivacaine followed by catheter-based infusions *vs.* Control group: IV analgesia (ketorolac, morphine)	Reduced mean pain scores of the chest at rest and during coughing in the study group (p=0.001). Reduced mean VAS scores of the ear in the study group (p=0.001).	Reduced amount of rescue IV ketorolac during the first 48 PO hours in the study group (p=0.026)
89	Lee JU et al. 2010	2-15 years	N=241 Control Group, n=120 Study Group, n=121	Ambulatory surgery: operations on their tonsil, ear, urinary tract, digestive tract etc. Control group: IV sulpyrin and/or meperidine postoperatively *vs.* Study group: regional nerve blockade with bupivacaine 0.25% + preoperatively rectally paracetamol 45 mg/kg or diclofenac 1 mg/kg	Reduced pain intensity in the Study Group (p<0.01)	----------

RCTs: Randomized Controlled Trials; NR: Number of Reference; NS: Non-significant Difference; FPS: Faces Pain Scale; PO: Postoperative; CHEOPS: the Children's Hospital of Eastern Ontario Pain Scale; OPS: Observational Pain Scale; GAN–block: Great Auricular Nerve Block; PACU: Post- Anaesthesia Care Unit; CHIPPS: Children and Infants Postoperative Pain Scale; ICNB: Intercostal Nerve Block; VAS: Visual Analogue Scale; IV: Intravenous

findings of our review. Dexmedetomidine is served as an excellent adjuvant by involving both peripheral and central mechanisms producing antinociception. Furthermore, it has significant opioid sparing effect. These characteristics can make this agent a valuable tool against postoperative pain and against the development of intractable neuropathic pain (by preventing hypersensitivity), as well.

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