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Ketamine for Perioperative Pain Management in Children.

A Meta Analysis of Published studies.

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For Peer Review

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3 Abstract
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5 Introduction: Balanced analgesia, using both opioid and non-opioids agents, has become the
6 standard care for postoperative pain management. Ketamine, a compound with analgesic and
7 antihyperalgesic properties, has been shown to decrease postoperative pain and opioid
8 requirements in adults. The goal of the present meta analysis was to investigate postoperative
9 analgesic properties of ketamine in pediatric patients.
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17 Material and Methods: A comprehensive literature search was conducted to identify clinical
18 trials that used ketamine as a perioperative analgesic compound in children and infants.

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22 Outcomes measured were: postoperative analgesic consumption, pain intensity and duration
23 of sensory block (when ketamine was used by caudal route) during the PACU (Postoperative
24 Care Unit) stay and the early postoperative period (6 to 24 hours after leaving the operative
25 room). The data from each trial were combined to calculate the pooled odds ratios or standard
26 mean differences and their 95% confidence intervals.
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34 Results: Thirty five randomized, blinded controlled studies were retrieved from the literature.
35 Systemic ketamine was effective in decreasing PACU pain intensity and analgesic
36 requirement but failed to influence early (6 to 24 hours) pain intensity and analgesic
37 requirement. Ketamine administered locally during tonsillectomy, decreased PACU and early
38 (6 to 24 hours) pain intensity and PACU analgesic requirements. Used as an adjuvant for
39 caudal analgesia, ketamine increased the duration of sensory block and PACU analgesic
40 requirement without impacting PACU pain intensity. Ketamine failed to exhibit a
41 postoperative opioid-sparing effect.
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53 Conclusions: This meta analysis found that administration of ketamine was associated with
54 decreased PACU postoperative pain intensity and non-opioid analgesic requirement.
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57 However, ketamine failed to exhibit a postoperative opioid-sparing effect.
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A Meta Analysis of Published studies.

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53 Conclusions: This meta analysis found that administration of ketamine was associated with
54 decreased PACU postoperative pain intensity and non-opioid analgesic requirement.
55 However, ketamine failed to exhibit a postoperative opioid-sparing effect.
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Introduction

Postoperative pain treatment has become a major concern in pediatric anesthesia^{1,2}. Although effective analgesics and age specific pain evaluation tools are available^{3,4}, postoperative pain is still undertreated in children^{1,2}.

Many studies have found pain to cause central nervous system sensitization. Memory of pain has been shown to exacerbate both present and future pain experiences. Moreover, some analgesic medications used in the perioperative setting, such as opioids, have also been found to cause postoperative sensitization⁵. Amongst neurobiological events involved in this phenomenon, the long term potentiation, initiated by NMDA receptor activation is one of the most important^{6,7}. Consequently, the use of NMDA antagonists, such as ketamine, has been hypothesized to counteract sensitization and produce an analgesic-sparing effect. Intravenous ketamine has been found to produce both analgesic and anti-sensitization effects in adult patients^{8,9}. However, its efficacy in children is still controversial. The analgesic efficacy of ketamine has also been studied both locally, during tonsillectomy and during epidural analgesia in children. However, no study has been undertaken to review the evidence from these studies.

Meta-analysis of published studies is a statistical methodology allowing aggregation and quantification of the therapeutic effects from multiple studies. It is particularly interesting when conflicting results arise from multiple studies. To date no meta analysis has been specifically performed on the efficacy of ketamine in the pediatric population. Thus, the goal of the present work was to perform a meta-analysis of the efficacy of ketamine in the management of postoperative pain in children when used by systemic, local or epidural routes.

Material and Methods

Bibliographic search and analysis

We conducted this meta-analysis according to the guidelines of the Cochrane Handbook for Systematic Reviews^a of intervention and the QUORUM statements¹⁰.

Literature databases included Pubmed and Embase. The following queries were used: "ketamine or ketalar and children or infant ". In addition, a manual search of the references found in the selected articles (including reviews and meta-analysis) was also performed. The articles obtained from these queries were independently analyzed by four anesthesiologists and those meeting the following criteria were included in the analysis: randomized controlled study, double blinded, absence of neurological and/or psychiatric diseases, standardized anesthesia protocol, standardized analgesic administration (including rescue analgesics), and presence of a control group. In addition, congress abstracts were not included in the analysis in order to assess the quality of studies. These strong criteria allowed selections of articles with lowest methodological bias. The date of the most recent search was February 2010.

Readers assessed articles quality and extracted data. These data consisted of: patient's ages, performed surgery, sedative premedication (dose, timing and route of administration), ketamine administration (route, doses, and timing), hypnotic agents used, intraoperative analgesia, postoperative analgesia. Outcomes analyzed were: postoperative pain (pain scores or percentage of patients experiencing moderate to severe pain), postoperative analgesic requirements (either doses or percentage of patient receiving postoperative treatments), postoperative (24 hours) opioid consumption (morphine or codeine), duration of regional analgesia (defined by the time to first complaint of pain when ketamine was administered by caudal route), time to first analgesic administration (opioids or non opioids analgesics

^a <http://www.cochrane-handbook.org/>. Last access December 2010.

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2
3 administered with a defined pain intensity target during caudal ketamine administration),
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5 postoperative nausea and vomiting (percentage of patients), and the occurrence of psycho-
6
7 mimetic manifestations such as nightmares or hallucinations (percentage of patients). When
8
9 conflicting results were found, the article was checked twice by the two anesthesiologists.
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12

13 14 15 *Statistical analysis*

16
17 Statistical analyses were performed using the Review Manager 5 software (RevMan 5, The
18
19 Cochrane Collaboration, Oxford, United Kingdom). When original data were expressed as
20
21 continuous variables, meta analysis was performed using the standardized mean difference
22
23 (SMD). This method allowed aggregation of outcomes measured using different tools. This
24
25 statistical method is especially pertinent to pediatric pain which is assessed using different
26
27 pain scales such as the OPS or EDIN scales^{11,12}. In all other cases, outcome incidence analysis
28
29 was performed using the odds ratio (OR) calculated using the Mantel-Haenszel method. In
30
31 order to include a maximum of appropriate studies, incomplete data were managed by
32
33 contacting the corresponding author or estimation of the mean and the SD on the basis of the
34
35 sample size, median, and range according to the method described by Hozo SP and
36
37 collaborators¹³. The absence of a validated method to convert median, interquartile ranges to
38
39 means, sd, lead us to discard all the data expressed in such a way. In articles where outcomes
40
41 were expressed as continuous values, a partial standardized mean ratio was initially computed
42
43 for each study, than transformed to partial ORs using Chinn's formulae¹⁴: $\text{LnOR} = 1.814 \times$
44
45 SMR (Ln : logarithm). The data were then entered as Ln(OR) and SD(LnOR) in the software.
46
47 Overall OR (and its 95% confidence interval) was then calculated using the inverse variance
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49 method^b.
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57 Heterogeneity was assessed using I^2 statistics. This describes the percentage of the variability
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^b <http://www.cochrane-handbook.org/> (Section 9.4.6). Last access December 2010.

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3 in effect estimates (OR or SMD) that is due to heterogeneity rather than sampling error.
4
5 According to the Cochrane review guidelines^c, an $I^2 > 40\%$ and a $p < 0.1$ were considered as
6
7 the threshold for heterogeneity and indicated the use of a random effect in OR and SMD
8
9 computation rather than a fixed effect model. Random effect model assumes that the observed
10
11 effects are estimating different intervention effects while a fixed effect model estimates the
12
13 same “true” intervention effect. This difference makes the weight given for each study
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15 different. In the random effect model all studies are equally weighted while in the fixed effect
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17 model each study is weighted according to the number of included patients. In addition,
18
19 subgroup analyses for ketamine efficacy were performed (when at least two studies included
20
21 the considered outcome) according to the administration regime (bolus or continuous) and the
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23 use of perioperative opioid agents. The effects of the racemic or the S(+) forms of ketamine
24
25 were also investigated.

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27 In studies with more than one intervention arm, each one was considered as a study and
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29 compared to the control group. Finally, to avoid calculation problems related to zero values, a
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31 1 was added to all groups^d.

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33 Statistical methodologies are available to assess the effects of unpublished studies on the
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35 results of meta-analysis (published bias). This type of bias is assessed by plotting the odds
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37 ratio (OR), or the logarithm of the OR, against a measurement of the precision of the OR such
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39 as the standard error of the OR. This plot is named the Funnel plot. An asymmetry of the
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41 Funnel plot could indicate that some studies might have been unpublished because their
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43 negative results^{c,15}. This asymmetry can also indicate the heterogeneity of results or the poor
44
45 methodology of included studies^{15,16}. Some published studies, due to specific design, can
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47 produce large positive results that can lead to asymmetry in the Funnel plots interpreted as
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49 “publication bias”. Methodological bias of studies can also exhibit large positive results
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^c <http://www.cochrane-handbook.org/> (Section 9.5.2). Last access December 2010.

^d <http://www.cochrane-handbook.org/> (Section 16.9.2). Last access December 2010.

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3 leading to funnel plot asymmetry^{15,17}. According to the Cochrane collaborative guideline^e
4 publication bias can be assessed when analysis aggregating at least 10 studies. Two tests were
5 used in the current analysis the Begg-Mazumdar¹⁸ and Egger tests¹⁷. When these tests are
6 significant, asymmetry is assumed to be present and publication bias is highly suspected.
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8 Results were expressed as OR, MD or SMD [95 % confidence interval], I², p value for I²
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^e <http://www.cochrane-handbook.org/> (Section 10.4.3.1). Last access December 2010.

Results

151 articles were identified using the selected criteria. Analysis allowed the selection of 53 relevant articles. The details of the selection process are summarized in figure 1. Publications with no control groups, cohort observational studies, studies comparing ketamine to other therapeutics and finally studies with non exploitable results (data expressed as median and interquartiles ranges) were excluded from this meta analysis (figure 1).

This meta analysis included 35 articles. The administration route for ketamine was systemic in 18 articles (567 patients received ketamine *versus* 418 did not received it)¹⁹⁻³⁶ (table 1); local or topical during tonsillectomy in 4 studies (125 patients received ketamine *versus* 100 did not received it)^{20,37-39} (table 2) and as an adjuvant to local anesthetics or opioid during caudal analgesia in 13 articles (392 patients received ketamine *versus* 323 did not received it)⁴⁰⁻⁵² (table 3).

Systemic route ketamine

All included studies used racemic ketamine as either a single bolus or as a bolus plus an intraoperative continuous administration, except in two studies^{32,53} in which ketamine was administered continuously both intra and postoperatively (table 1). Efficacy outcomes included pain intensity scores and analgesic requirements, both during the PACU stay (the first two hours) and the early postoperative period (between 6 and 24 hours). These two ranges were defined based on individual study results to maximize the data included in the meta analysis. Ketamine was associated with a decrease in PACU postoperative pain scores and analgesic requirements (figures 2A and 2B, respectively). However, it failed to improve early postoperative pain intensity and analgesic requirements (figures 3A and 3B, respectively). Analyzing studies that reported cumulative opioid administration during the

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3 first 24 hours postoperatively found that ketamine was not associated with an opioid-sparing
4 effect during this period (figure 4).
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8 The Results of the overall analysis did not take in account interventions performed, single
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10 bolus versus continuous administration of ketamine or preoperative or postoperative
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12 analgesics used (opioids *versus* non opioids). This is reflected by the high heterogeneity of the
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14 results obtained by pooling all studies. Consequently, subgroup analyses were indicated.
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16 Analysis of ketamine efficacy according to the intraoperative, postoperative or perioperative
17 (intra and postoperative periods) opioid use, showed this factor to influence analyzed
18 outcomes (table 4). When opioid agents were used, results were similar to the overall analyses
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20 (decrease in PACU pain intensity and analgesic requirement, without impacting upon early
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22 outcomes). Conversely, when anesthesia and/or postoperative analgesia did not involve opioid
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24 agents, ketamine decreased early postoperative pain scores and early analgesic requirements
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26 without impacting nor PACU pain scores neither PACU analgesic requirements (table 4). All
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28 the included studies used intraoperative Nitrous Oxide (N₂O). Consequently, the effect of this
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30 agent on ketamine efficacy could not be analyzed.
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34 Analyzing studies involving tonsillectomy, found an efficacy of ketamine on pain scores and
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36 analgesic requirements during the PACU and the early postoperative stages (table 4).
37
38 Ketamine was only effective in decreasing the PACU postoperative pain when used during
39
40 abdominal, orthopedic or urologic surgeries (table 4).
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44 Bolus mode was effective in decreasing PACU postoperative pain intensities and analgesia
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46 requirements and early postoperative pain intensities, while bolus plus continuous infusion
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48 failed to improve the postoperative pain or decrease analgesic requirement during neither the
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50 PACU nor the early postoperative stages (table 4).
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54 Concerning the adverse effects, ketamine given intravenously was not associated with
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56 postoperative nausea and vomiting (during the first 24 postoperative hours) or psycho-
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3 mimetic manifestations (OR = 1.35 [0.99, 2.09], $I^2 = 0\%$, $p = 0.52$; OR = 1.52 [0.72, 3.24], I^2
4 = 0%, $p = 0.96$; respectively).

5
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7 Analysis found no evidence of publication bias for all the following outcomes: PACU pain
8 intensities (Begg-Mazumbar test : Kendall's Tau = -0.09 $p = 0.65$ or Egger's test : bias = -2.3,
9 $p = 0.58$), early pain intensities (Begg-Mazumbar test : Kendall's Tau = -0.09 $p = 0.71$ or
10 Egger's test : bias = -1.12, $p = 0.$), early analgesic consumption (Begg-Mazumbar test :
11 Kendall's Tau = -0.2 $p = 0.32$ or Egger's test : bias = -1.7, $p = 0.39$), postoperative nausea
12 and vomiting (Begg-Mazumbar test : Kendall's Tau = -0.09 $p = 0.70$ or Egger's test : bias = -
13 0.2, $p = 0.87$) or psycho-mimetic manifestations (Begg-Mazumbar test : Kendall's Tau = -
14 0.27, $p = 0.29$ or Egger's test : bias = -1.17, $p = 0.18$).

25 26 27 28 29 *Local or topical ketamine during adenotonsillectomy*

30
31 All the included studies used the racemic form of ketamine either by local infiltration
32 in the surgical field or by a topical application during adenotonsillectomy (table 2). Efficacy
33 outcomes analyzed were: PACU (the two first hours) pain scores and analgesic requirements
34 and early pains scores and analgesic requirements (between 6 and 24 hours). Ketamine
35 decreased PACU pain scores and analgesic requirements (figure 5A and 5B, respectively).
36 Concerning early outcomes, ketamine decreased pain scores without impacting early
37 analgesic requirements (figure 6A and 6B, respectively).

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48 Given the number and characteristics of the included studies, subgroup analysis could not be
49 performed. All the included studies used intraoperative N₂O. Consequently, the effect of this
50 agent on ketamine efficacy could not be analyzed.

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55 Locally administered ketamine was not associated with an increased incidence of PONV or
56 psycho-mimetic manifestations (OR = 0.60 [0.28, 1.29], $I^2 = 0\%$, $p = 0.49$; 1.00 [0.28, 3.55],
57 $I^2 = 0\%$, $p = 1$; respectively).

Ketamine as an adjuvant during caudal analgesia

When given as an adjuvant during caudal analgesia, racemic and S(+) ketamine increased the block duration (figure 7A) and decreased analgesics requirement in the PACU (figure 7B). However, it failed to decrease pain intensity at admission to the PACU and at 60, 180 and 360 minutes postoperatively (figures 8A, 8B, 8C and 8D, respectively).

Subgroup analysis according to the racemic forms of ketamine, found no influence of the racemic or S+ form on the results (table 5). However, when analysis included studies using intraoperative, postoperative or perioperative opioids, postoperative analgesic requirements were equivalent in the ketamine and the control arms (table 5). Conversely, when studies involving only non-opioid analgesics were analysed, ketamine exhibited superiority over controls (table 5). All the included studies used intraoperative N₂O. Consequently, the effect of this agent on ketamine efficacy could not be analyzed.

Neither the occurrence of PONV nor that of psycho-mimetic manifestations were influenced by ketamine administration (OR = 1.17 [0.69, 1.98], I² = 0 %, p = 0.83 and 1.72 [0.69, 4.26], I² = 0 %, p = 0.97, respectively).

Analysis found no evidence of publication bias for all the following outcomes: block duration (Begg-Mazumbar test : Kendall's Tau = 0.3, p = 0.19 or Egger's test : bias = 11.5, p = 0.06), analgesic consumption (Begg-Mazumbar test : Kendall's Tau = -0.3, p = 0.17 or Egger's test : bias = -3.99, p = 0.07), postoperative nausea and vomiting (Begg-Mazumbar test : Kendall's Tau = -0.06, p = 0.73 or Egger's test : bias = -1.15, p = 0.41), motor block (Begg-Mazumbar test : Kendall's Tau = 0.08, p = 0.75 or Egger's test : bias = -1.16, p = 0.4) or urinary retention (Begg-Mazumbar test : Kendall's Tau = 0, p = 0.9 or Egger's test : bias = 0.02, p = 0.9).

Discussion

The main finding of this meta analysis can be summarized as follows: used systemically, ketamine was effective in decreasing pain intensity and analgesic requirements during the PACU stay but not during the early postoperative period (6 to 24 hours). However, used locally during tonsillectomy, ketamine decreased both PACU and early (6 to 24 hours) postoperative analgesic requirement. Finally, used as caudal analgesia adjuvant, it increased the duration of sensory block and improved pain relief at emergence without influencing pain scores in PACU.

The subgroup analysis of studies using opioid analgesics either intra and/or postoperatively, found systemic ketamine to have no impact upon early postoperative pain intensity or analgesic requirement. In contrast, studies without intra and/or postoperative opioid administration showed systemic ketamine to reduce early pain intensity and analgesic requirement (table 4).

Insufficient ketamine dosage and/or administration regimen might explain the lack of efficacy of ketamine when co administered with opioid agents or when administered continuously (table 4). Most studies performed in adults have used ketamine as a continuous administration during the perioperative period^{9,54}. Perioperative continuous administration was found in two studies included in our meta analysis^{32,53}. Additionally, ketamine doses were similar to, and in some cases lower than, those used in adults⁵⁴, whilst pharmacokinetic and pharmacodynamic studies in children and adults indicate a faster pharmacokinetics (The context-sensitive half-time in children (10 kg) after 1.5 h, rising from 30 min at 1 h to 55 min at 5 h at 3 mgxk⁻¹gxh⁻¹, the context-sensitive half-time in adults was 23 min at 1 h and 83 min at 5 h at the same infusion rate⁵⁵) and a lower sensitivity in pediatric populations when compared to adults (concentrations of ketamine at awakening in children and adults were 0.9 to 3.8 mgxL⁻¹ and 0.5 mgxL⁻¹, respectively^{56,57}). Consequently, future studies have to focus on

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2
3 doses of ketamine adapted to the pharmacology of this agent in children. These
4
5 pharmacologic considerations might also explain the absence of an opioid-sparing effect of
6
7 ketamine. Alternatively, this result can also be explained by studies reviewed that included
8
9 few cases of major intracavitary or major orthopedic surgeries (table 1). Another concern
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11 about the absence of an opioid-sparing effect observed in our study was the possibility of
12
13 underestimation of pain and systematic pre-emptive analgesia that might misestimate the true
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15 opioid requests. However, this is very unlikely while postoperative opioids were given by
16
17 care givers according to pain evaluation scales (table 1). Pain scales used in the included
18
19 studies (OPS¹¹, EDIN¹², CHEOPS⁵⁸ scores, analog visual and verbal numerical scales⁵⁹) were
20
21 another concern in the interpretation of our results. These scales were not validated during
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23 ketamine administration either alone or in association with other analgesics and they can not
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25 discriminate the analgesia from the sedation observed after ketamine administration^{11,12}.
26
27 Consequently, the effects of ketamine observed in the absence of opioid administration might
28
29 be due to the sedative effect of this agent rather than to its analgesic effects.
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36 Ketamine has been shown experimentally to antagonize NMDA and opioid receptors⁶⁰⁻⁶². The
37
38 absence of ketamine effects on early (6 to 24 hours) pain intensity and analgesic requirement
39
40 when opioid were used might be explained by the absence of ketamine opioid receptors
41
42 modulation in the presence of opioids. This hypothesis is supported by the higher affinity of
43
44 opioids agents to the opioids receptors (for example, K_i values of ketamine and morphine to
45
46 inhibit the binding of [³H]diprenorphine to μ -opioid receptors were 2.6×10^6 and 24.80 nM
47
48 respectively^{61,63,64}). However, this hypothesis seems very unlikely in this context while it is
49
50 inconsistent with previous works that found NMDA receptors antagonism as the major
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52 mechanism of ketamine antihyperalgesia^{65,66}. In addition, this hypothesis cannot give a
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54 satisfactory explanation about the difference in analgesic properties of ketamine in children
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56 and adults^{8,9}.
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3 We chose to analyze separately the local ketamine effects, although, its analgesic
4 efficacy could result from a systemic action. There has been a recent criticism of the local use
5 of ketamine because of the possibility of an increased risk of postoperative hematoma and
6 bleeding after peritonsillar ketamine infiltration ⁶⁷. Local administration of ketamine during
7 tonsillectomy decreased both the PACU and the early postoperative pain and produced an
8 analgesic-sparing effect during the PACU period. No other benefice of local ketamine during
9 this surgery could be analyzed.

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20 Our results showed that caudal ketamine was effective in reducing the emergence pain and in
21 increasing the duration of sensory block without influencing pain intensity (until the 360
22 postoperative minutes). This fact suggests that in this type of surgery, the effect of caudal
23 ketamine was relatively weak on epidural analgesia. Interestingly, the administration of S(+)
24 ketamine, a more potent form than the racemic ketamine^{68,69}, failed to decrease analgesic
25 requirement in the PACU. Its rapid pharmacokinetics, in comparison to the racemic product
26 (clearances of S(+) ketamine and R(-) ketamine are 19.1 ± 7.2 and 16.5 ± 4.8 $\text{ml} \times \text{min}^{-1} \times \text{Kg}^{-1}$,
27 respectively⁷⁰), could explain this result. Finally, postoperative systemic opioid administration
28 totally blunts the analgesic sparing effect of caudal ketamine (table 5). This result can be
29 explained by the weak effect of caudal ketamine. Otherwise, the competition of opioid agents
30 and ketamine on opioid receptors, described experimentally, might also account in this result.
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Meta-analysis quality relies on three major factors. Firstly, the quality of selected
studies; secondly the heterogeneity of results; and lastly the detection of publication bias.
Studies included in this analysis met very strict criteria as detailed in Material and Methods.

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3 These strict selection criteria were very likely to decrease the methodological bias of each
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5 study included in the analysis¹⁵.
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8 The methodological plan used in this review was applied to take into account the
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10 heterogeneity of studies. Subgroup analyses were performed to decrease the heterogeneity and
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12 to identify factors influencing the results. This goal was partially achieved with the analysis of
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14 the systemic ketamine administration. Conversely, despite subgroup analyses, this was not
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16 possible for the caudal administration of ketamine. One factor that might have caused the high
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18 heterogeneity was the variability of the sensory block.
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22 Using two statistical tools, we found no significant publication bias. In addition, publication
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24 bias was unlikely to have been a problem in the present analysis because it is usually the case
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26 that unpublished studies are those with negative outcomes. The conclusions of this review
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28 were in large part negative, so the absence of more negative data might have little effect on
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30 the outcome of this analysis.
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34 In conclusion, this meta analysis demonstrated the safety of ketamine. During
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36 systemic, local or caudal administration of ketamine, the analgesic effect of this compound
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38 was observed in the PACU period and was not associated with an opioid-sparing effect.
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40 Ketamine decreased early (6 to 24 hours) pain intensity and non-opioid analgesic
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42 requirements only when no opiates were given.
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3 Acknowledgement
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9
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Legends of tables and figures

Table 1: Characteristics of included studies using systemic ketamine. (IH : Inguinal Hernia, Circ : Circumcision; PCA : Patient Controlled Analgesia).

Table 2: Characteristics of included studies using local or topic ketamine.

Table 3: Characteristics of included studies using caudal ketamine. (IH : Inguinal Hernia, Circ : Circumcision; Orch : orchidopexia).

Table 4: Subgroup analysis of the effects of surgeries, opioid analgesics and the administration regime on the analgesic efficacy of intravenous ketamine. Data are expressed as odds ratio (OR) or standard mean difference (SMD) with the 95 % confidence interval (CI), I^2 , p for I^2 . NP: not performed. Results in bold indicate significant effect of ketamine on the studied outcome. * indicate the use of a random effect model in OR or SMD computation.

Table 5: Subgroup analysis of the effects of the racemic form of ketamine and the opioids analgesia on the analgesic efficacy of caudal ketamine. Data are expressed as odds ratio (OR) or standard mean difference (SMD) with the 95 % confidence interval (CI), I^2 , p for I^2 . Results in bold indicate significant effect of ketamine on the studied outcome. * indicate the use of a random effect model in OR or SMD computation.

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3 Figure 1: Meta analysis flowchart. RTC: randomized controlled trials.
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8 Figure 2: Forest plot of meta-analysis of the effects of intravenous ketamine on postoperative
9 care unit (2 hours) postoperative pain scores (A) and analgesic requirements (B). The square
10 in front of each study (first author and year of publication) is the odds ratio (OR) or the
11 standard mean difference (SMD) for individual trials, and the corresponding horizontal line is
12 the 95% confidence interval (CI). The lozenge back in the figure is the pooled OR or SMD
13 with the 95 % confidence interval (CI). Studies with more than one intervention group were
14 starred (Author, year of publication* and Author, year of publication **).
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27 Figure 3: Forest plot of meta-analysis of the effects of intravenous ketamine on early (6 to 24
28 hours) postoperative pain scores (A) and analgesic requirements (B). The square in front of
29 each study (first author and year of publication) is the odds ratio (OR) for individual trials,
30 and the corresponding horizontal line is the 95% confidence interval (CI). The lozenge back
31 in the figure is the pooled OR with the 95 % confidence interval (CI). Studies with more than
32 one intervention group were starred (Author, year of publication* and Author, year of
33 publication **).
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46 Figure 4: Forest plot of meta-analysis of the effects of intravenous ketamine on postoperative
47 opioids consumption during the first 24 postoperative hours. The square in front of each study
48 (first author and year of publication) is the odds ratio (OR) for individual trials, and the
49 corresponding horizontal line is the 95% confidence interval (CI). The lozenge back in the
50 figure is the pooled OR with the 95 % confidence interval (CI).
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60 Figure 5: Forest plot of meta-analysis of the effects of local or topic ketamine on
postoperative care unit postoperative pain scores (A) and analgesic requirements (B). The

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3 square in front of each study (first author and year of publication) is the odds ratio (OR) or the
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5 standard mean difference (SMD) for individual trials, and the corresponding horizontal line is
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7 the 95% confidence interval (CI). The lozenge back in the figure is the pooled OR or SMD
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9 with the 95 % confidence interval (CI). Studies with more than one intervention group were
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11 starred (Author, year of publication* and Author, year of publication **).

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17 Figure 6: Forest plot of meta-analysis of the effects of local or topic ketamine on early (6 to
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19 24 hours) postoperative pain scores (A) and analgesic requirements (B). The square in front of
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21 each study (first author and year of publication) is the odds ratio (OR) or the standard mean
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23 difference (SMD) for individual trials, and the corresponding horizontal line is the 95%
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25 confidence interval (CI). The lozenge back in the figure is the pooled OR or SMD with the 95
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27 % confidence interval (CI). Studies with more than one intervention group were starred
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29 (Author, year of publication* and Author, year of publication **).

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36 Figure 7: Forest plot of meta-analysis of the effects of caudal ketamine on sensory block
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38 duration (A) and analgesic requirements (B). The square in front of each study (first author
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40 and year of publication) is the odds ratio (OR) or the standard mean difference (SMD) for
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42 individual trials, and the corresponding horizontal line is the 95% confidence interval (CI).
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44 The lozenge back in the figure is the pooled OR or SMD with the 95 % confidence interval
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46 (CI). Studies with more than one intervention group were starred (Author, year of
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48 publication* and Author, year of publication **).

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55 Figure 8: Forest plot of meta-analysis of the effects of caudal ketamine on pain intensities at
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57 PACU admission (A) and 60 minutes (B), 180 minutes (C) and 360 minutes (D) after PACU
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59 admission. The square in front of each study (first author and year of publication) is the odds
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ratio (OR) for individual trials, and the corresponding horizontal line is the 95% confidence

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3 interval (CI). The lozenge back in the figure is the pooled OR with the 95 % confidence
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5 interval (CI). Studies with more than one intervention group were starred (Author, year of
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7 publication* and Author, year of publication **).

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References

1. Astuto M, Rosano G, Rizzo G, Disma N, di Cataldo A: Methodologies for the treatment of acute and chronic nononcologic pain in children. *Minerva Anestesiologica* 2007; 73: 459-465
2. Morton NS: Management of postoperative pain in children. *Arch Dis Child Educ Pract Ed* 2007; 92: ep14-9
3. Anderson KO: Assessment tools for the evaluation of pain in the oncology patient. *Curr Pain Headache Rep* 2007; 11: 259-64
4. Hain RD: Pain scales in children: a review. *Palliat Med* 1997; 11: 341-50
5. Lavand'homme P: Perioperative pain. *Curr Opin Anaesthesiol* 2006; 19: 556-61
6. Clivatti J, Sakata RK, Issy AM: Review of the use of gabapentin in the control of postoperative pain. *Rev Bras Anesthesiol* 2009; 59: 92-8, 87-92
7. De Kock MF, Lavand'homme PM: The clinical role of NMDA receptor antagonists for the treatment of postoperative pain. *Best Pract Res Clin Anaesthesiol* 2007; 21: 85-98
8. Bell G, Dickson U, Arana A, Robinson D, Marshall C, Morton N: Remifentanil vs fentanyl/morphine for pain and stress control during pediatric cardiac surgery. *Paediatric Anaesthesia* 2004; 14: 856-860
9. Elia N, Tramer MR: Ketamine and postoperative pain--a quantitative systematic review of randomised trials. *Pain* 2005; 113: 61-70
10. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF: Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. *Quality of Reporting of Meta-analyses. Lancet* 1999; 354: 1896-900
11. Hannallah RS, Broadman LM, Belman AB, Abramowitz MD, Epstein BS: Comparison of caudal and ilioinguinal/iliohypogastric nerve blocks for control of post-orchiopepy pain in pediatric ambulatory surgery. *Anesthesiology* 1987; 66: 832-4
12. Debillon T, Zupan V, Ravault N, Magny JF, Dehan M: Development and initial validation of the EDIN scale, a new tool for assessing prolonged pain in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2001; 85: F36-41
13. Hozo SP, Djulbegovic B, Hozo I: Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005; 5: 13
14. Chinn S: A simple method for converting an odds ratio to effect size for use in meta-analysis. *Stat Med* 2000; 19: 3127-31
15. Sterne JA, Egger M, Smith GD: Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ* 2001; 323: 101-5
16. Sutton AJ, Higgins JP: Recent developments in meta-analysis. *Stat Med* 2008; 27: 625-50
17. Egger M, Davey Smith G, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315: 629-34
18. Begg CB, Mazumdar M: Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50: 1088-101
19. Aydin ON, Ugur B, Ozgun S, Eyigor H, Copcu O: Pain prevention with intraoperative ketamine in outpatient children undergoing tonsillectomy or tonsillectomy and adenotomy. *Journal of Clinical Anesthesia* 2007; 19: 115-119
20. Dal D, Celebi N, Elvan EG, Celiker V, Aypar U: The efficacy of intravenous or peritonsillar infiltration of ketamine for postoperative pain relief in children following adenotonsillectomy. *Paediatric Anaesthesia* 2007; 17: 263-269
21. Da Conceicao MJ, Bruggemann Da Conceicao D, Carneiro Leao C: Effect of an intravenous single dose of ketamine on postoperative pain in tonsillectomy patients.

1
2
3 Paediatric Anaesthesia 2006; 16: 962-967

4 22. O'Flaherty JE, Lin CX: Does ketamine or magnesium affect posttonsillectomy pain in
5 children? Paediatric Anaesthesia 2003; 13: 413-421

6 23. Elhakim M, Khalafallah Z, El-Fattah HA, Farouk S, Khattab A: Ketamine reduces
7 swallowing-evoked pain after paediatric tonsillectomy. Acta Anaesthesiologica Scandinavica
8 2003; 47: 604-609

9 24. Murray WB, Yankelowitz SM, Le Roux M, Bester HF: Prevention of post-
10 tonsillectomy pain with analgesic doses of ketamine. South African Medical Journal 1987;
11 72: 839-842

12 25. Kararmaz A, Kaya S, Turhanoglu S, Ozyilmaz MA: Oral ketamine premedication can
13 prevent emergence agitation in children after desflurane anaesthesia. Paediatric Anaesthesia
14 2004; 14: 477-482

15 26. Umuroglu T, Eti Z, Ciftci H, Yilmaz Gogus F: Analgesia for adenotonsillectomy in
16 children: A comparison of morphine, ketamine and tramadol. Paediatric Anaesthesia 2004;
17 14: 568-573

18 27. Abu-Shahwan I: Ketamine does not reduce postoperative morphine consumption after
19 tonsillectomy in children. The Clinical journal of pain 2008; 24: 395-398

20 28. Batra YK, Shamsah M, Al-Khasti MJ, Rawdhan HJ, Al-Qattan AR, Belani KG:
21 Intraoperative small-dose ketamine does not reduce pain or analgesic consumption during
22 perioperative opioid analgesia in children after tonsillectomy. Int J Clin Pharmacol Ther
23 2007; 45: 155-60

24 29. Tarkkila P, Viitanen H, Mennander S, Annila P: Comparison of remifentanil versus
25 ketamine for paediatric day case adenoidectomy. Acta Anaesthesiol Belg 2003; 54: 217-22

26 30. Zahra FA, Abudallah HM, Shabana RI, Abdulmageed WM, Abdulrazik SI, Nassar
27 AM: Intramuscular ketamine for prevention of postanesthesia shivering in children. Saudi
28 Med J 2008; 29: 1255-9

29 31. Dix P, Martindale S, Stoddart PA: Double-blind randomized placebo-controlled trial
30 of the effect of ketamine on postoperative morphine consumption in children following
31 appendicectomy. Paediatric Anaesthesia 2003; 13: 422-426

32 32. Engelhardt T, Zaarour C, Naser B, Pehora C, de Ruiten J, Howard A, Crawford MW:
33 Intraoperative low-dose ketamine does not prevent a remifentanil-induced increase in
34 morphine requirement after pediatric scoliosis surgery. Anesth Analg 2008; 107: 1170-5

35 33. Butkovic D, Kralik S, Matolic M, Jakobovic J, Zganjer M, Radesic L: Comparison of
36 a preincisional and postincisional small dose of ketamine for postoperative analgesia in
37 children. Bratislavske lekarske listy 2007; 108: 184-188

38 34. Darabi ME, Mireskandari SM, Sadeghi M, Salamati P, Rahimi E: Ketamine has no
39 pre-emptive analgesic effect in children undergoing inguinal hernia repair. Acta Medica
40 Iranica 2008; 46: 451-456

41 35. Inanoglu K, Ozbakis Akkurt BC, Turhanoglu S, Okuyucu S, Akoglu E: Intravenous
42 ketamine and local bupivacaine infiltration are effective as part of a multimodal regime for
43 reducing post-tonsillectomy pain. Med Sci Monit 2009; 15: CR539-543

44 36. Bazin V, Bollot J, Asehnoune K, Roquilly A, Guillaud C, De Windt A, Nguyen JM,
45 Lejus C: Effects of perioperative intravenous low dose of ketamine on postoperative analgesia
46 in children. Eur J Anaesthesiol 2010; 27: 47-52

47 37. Honarmand A, Safavi MR, Jamshidi M: The preventative analgesic effect of
48 preincisional peritonsillar infiltration of two low doses of ketamine for postoperative pain
49 relief in children following adenotonsillectomy. A randomized, double-blind, placebo-
50 controlled study. Paediatr Anaesth 2008; 18: 508-14

51 38. Canbay O, Celebi N, Uzun S, Sahin A, Celiker V, Aypar U: Topical ketamine and
52 morphine for post-tonsillectomy pain. European Journal of Anaesthesiology 2008; 25: 287-
53 292

- 1
- 2
- 3 39. Erhan OL, Goksu H, Alpay C, Bestas A: Ketamine in post-tonsillectomy pain. *Int J*
- 4 *Pediatr Otorhinolaryngol* 2007; 71: 735-9
- 5
- 6 40. Akbas M, Titiz TA, Ertugrul F, Akbas H, Melikoglu M: Comparison of the effect of
- 7 ketamine added to bupivacaine and ropivacaine, on stress hormone levels and the duration of
- 8 caudal analgesia. *Acta Anaesthesiol Scand* 2005; 49: 1520-6
- 9
- 10 41. De Negri P, Ivani G, Visconti C, De Vivo P: How to prolong postoperative analgesia
- 11 after caudal anaesthesia with ropivacaine in children: S-ketamine versus clonidine. *Paediatr*
- 12 *Anaesth* 2001; 11: 679-83
- 13
- 14 42. Gunes Y, Secen M, Ozcengiz D, Gunduz M, Balcioglu O, Isik G: Comparison of
- 15 caudal ropivacaine, ropivacaine plus ketamine and ropivacaine plus tramadol administration
- 16 for postoperative analgesia in children. *Paediatric Anaesthesia* 2004; 14: 557-563
- 17
- 18 43. Kumar P, Rudra A, Pan AK, Acharya A: Caudal additives in pediatrics: A comparison
- 19 among midazolam, ketamine, and neostigmine coadministered with bupivacaine. *Anesthesia*
- 20 *and analgesia* 2005; 101: 69-73
- 21
- 22 44. Lee HM, Sanders GM: Caudal ropivacaine and ketamine for postoperative analgesia in
- 23 children. *Anaesthesia* 2000; 55: 806-810
- 24
- 25 45. Locatelli BG, Frawley G, Spotti A, Ingelmo P, Kaplanian S, Rossi B, Monia L,
- 26 *Sonzogni V: Analgesic effectiveness of caudal levobupivacaine and ketamine. British Journal*
- 27 *of Anaesthesia* 2008; 100: 701-706
- 28
- 29 46. Ozbek H, Bilen A, Ozcengiz D, Gunes Y, Ozalevli M, Akman H: The comparison of
- 30 caudal ketamine, alfentanil and ketamine plus alfentanil administration for postoperative
- 31 analgesia in children. *Paediatric Anaesthesia* 2002; 12: 610-616
- 32
- 33 47. Weber F, Wulf H: Caudal bupivacaine and s(+)-ketamine for postoperative analgesia
- 34 in children. *Paediatr Anaesth* 2003; 13: 244-8
- 35
- 36 48. Pathania J, Thakur JR, Sodhi SS: Comparison of efficacy and duration of caudal
- 37 analgesia produced by bupivacaine alone and in combination with adrenaline and ketamine in
- 38 children. *Journal of Anaesthesiology Clinical Pharmacology* 2003; 19: 207-211
- 39
- 40 49. Choudhuri AH, Dharmani P, Kumarl N, Prakash A: Comparison of caudal epidural
- 41 bupivacaine with bupivacaine plus tramadol and bupivacaine plus ketamine for postoperative
- 42 analgesia in children. *Anaesth Intensive Care* 2008; 36: 174-9
- 43
- 44 50. Naguib M, Sharif AM, Seraj M, el Gammal M, Dawlatly AA: Ketamine for caudal
- 45 analgesia in children: comparison with caudal bupivacaine. *Br J Anaesth* 1991; 67: 559-64
- 46
- 47 51. Pan AK, Rudra A: Caudal analgesia in paediatrics: Comparison between bupivacaine
- 48 alone and in combination with ketamine, midazolam and ketamine-midazolam. *Journal of*
- 49 *Anaesthesiology Clinical Pharmacology* 2005; 21: 401-405
- 50
- 51 52. Nafiu OO, Kolawole IK, Salam RA, Elegbe EO: Comparison of caudal ketamine with
- 52 or without bupivacaine in pediatric subumbilical surgery. *J Natl Med Assoc* 2007; 99: 670-3
- 53
- 54 53. Bazin V, Bollot J, Asehnoune K, Roquilly A, Guillaud C, De Windt A, Nguyen JM,
- 55 *Lejus C: Effects of perioperative intravenous low dose of ketamine on postoperative analgesia*
- 56 *in children. Eur J Anaesthesiol*; 27: 47-52
- 57
- 58 54. Subramaniam K, Subramaniam B, Steinbrook RA: Ketamine as adjuvant analgesic to
- 59 opioids: a quantitative and qualitative systematic review. *Anesth Analg* 2004; 99: 482-95,
- 60 *table of contents*
- 55 55. Dallimore D, Anderson BJ, Short TG, Herd DW: Ketamine anesthesia in children--
- 56 *exploring infusion regimens. Paediatr Anaesth* 2008; 18: 708-14
- 57
- 58 56. Idvall J, Ahlgren I, Aronsen KR, Stenberg P: Ketamine infusions: pharmacokinetics
- 59 and clinical effects. *Br J Anaesth* 1979; 51: 1167-73
- 60
- 57 57. Grant IS, Nimmo WS, McNicol LR, Clements JA: Ketamine disposition in children
- and adults. *Br J Anaesth* 1983; 55: 1107-11
- 58
- 59 58. Suraseranivongse S, Santawat U, Kraiprasit K, Petcharatana S, Prakkamodom S,
- 60 *Muntraporn N: Cross-validation of a composite pain scale for preschool children within 24*

1
2
3 hours of surgery. *Br J Anaesth* 2001; 87: 400-5

4 59. Bailey B, Daoust R, Doyon-Trottier E, Dauphin-Pierre S, Gravel J: Validation and
5 properties of the verbal numeric scale in children with acute pain. *Pain* 2010; 149: 216-21

6 60. Sarton E, Teppema LJ, Olievier C, Nieuwenhuijs D, Matthes HW, Kieffer BL, Dahan
7 A: The involvement of the mu-opioid receptor in ketamine-induced respiratory depression
8 and antinociception. *Anesth Analg* 2001; 93: 1495-500, table of contents

9 61. Hirota K, Okawa H, Appadu BL, Grandy DK, Devi LA, Lambert DG: Stereoselective
10 interaction of ketamine with recombinant mu, kappa, and delta opioid receptors expressed in
11 Chinese hamster ovary cells. *Anesthesiology* 1999; 90: 174-82

12 62. Minami K, Sudo Y, Shiraishi S, Seo M, Uezono Y: Analysis of the effects of
13 anesthetics and ethanol on mu-opioid receptor. *J Pharmacol Sci* 2010; 112: 424-31

14 63. Amiche M, Sagan S, Mor A, Pelaprat D, Rostene W, Delfour A, Nicolas P:
15 Characterisation and visualisation of [3H]dermorphin binding to mu opioid receptors in the
16 rat brain. Combined high selectivity and affinity in a natural peptide agonist for the morphine
17 (mu) receptor. *Eur J Biochem* 1990; 189: 625-35

18 64. Yu G, Yue YJ, Cui MX, Gong ZH: Thienorphine is a potent long-acting partial opioid
19 agonist: a comparative study with buprenorphine. *J Pharmacol Exp Ther* 2006; 318: 282-7

20 65. Lutfy K, Cai SX, Woodward RM, Weber E: Antinociceptive effects of NMDA and
21 non-NMDA receptor antagonists in the tail flick test in mice. *Pain* 1997; 70: 31-40

22 66. Hingne PM, Sluka KA: Blockade of NMDA receptors prevents analgesic tolerance to
23 repeated transcutaneous electrical nerve stimulation (TENS) in rats. *J Pain* 2008; 9: 217-25

24 67. Shah RK, Preciado DA: Re: the efficacy of intravenous or peritonsillar infiltration of
25 ketamine for postoperative pain relief in children following adenotonsillectomy. *Paediatric
26 Anaesthesia* 2007; 17: 1114-1115; author reply 1115

27 68. Pees C, Haas NA, Ewert P, Berger F, Lange PE: Comparison of analgesic/sedative
28 effect of racemic ketamine and S(+)-ketamine during cardiac catheterization in newborns and
29 children. *Pediatr Cardiol* 2003; 24: 424-9

30 69. Joo G, Horvath G, Klimscha W, Kekesi G, Dobos I, Szikszay M, Benedek G: The
31 effects of ketamine and its enantiomers on the morphine- or dexmedetomidine-induced
32 antinociception after intrathecal administration in rats. *Anesthesiology* 2000; 93: 231-41

33 70. Geisslinger G, Hering W, Thomann P, Knoll R, Kamp HD, Brune K:
34 Pharmacokinetics and pharmacodynamics of ketamine enantiomers in surgical patients using
35 a stereoselective analytical method. *Br J Anaesth* 1993; 70: 666-71

36 71. Boettger MK, Weber K, Gajda M, Brauer R, Schaible HG: Spinally applied ketamine
37 or morphine attenuate peripheral inflammation and hyperalgesia in acute and chronic phases
38 of experimental arthritis. *Brain Behav Immun* 2010; 24: 474-85

39 72. Kosson D, Klinowiecka A, Kosson P, Bonney I, Carr DB, Mayzner-Zawadzka E,
40 Lipkowski AW: Intrathecal antinociceptive interaction between the NMDA antagonist
41 ketamine and the opioids, morphine and buphalin. *Eur J Pain* 2008; 12: 611-6

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Authors, years	ASA	Age	Surgery	Ketamine (doses)	Ketamine S+	Timing of Ketamine	Premedication	Intraoperative analgesia	Postoperative analgesia	Pain evaluation scale or score used	Control of Analgesia	Preventive antiemetics
Dix P*, 2003 ³¹	I/II	7 to 16	Appendicectomy	0.5 mg/Kg	No	After induction	No	Fentanyl + Diclofenac + infiltration	PCA + Acetaminophen	VAS	PCA by self administration	No
Dix P**, 2003 ³¹	I/II	8 to 16	Appendicectomy	0.5 mk/Kg + 4µg/Kg/mn	No	After induction & postoperative	No	Fentanyl + Diclofenac + infiltration	PCA + Acetaminophen	VAS	PCA by self administration	No
Engelhardt T, 2008 ³²	I/II	12 to 18	Scoliosis	0.5 mk/Kg + 4µg/Kg/mn	No	After induction & peroperative	No	Remifentanil+Morphine	PCA	NRS	PCA by self evaluation	No
Butkovic D*, 2007 ³³	I/II	4 to 14	IH, Circ	0.3 mg/Kg	No	After induction	Midazolam	Diclofenac	Diclifenac	VAS	Nurses, Diclofenac given as needed by pain	No
Butkovic D*, 2007 ³³	I/II	5 to 14	IH, Circ	0.3 mg/Kg	No	End of surgery	Midazolam	Diclofenac	Diclifenac	VAS	Nurses, Diclofenac given as needed by pain	No
Darabi ME*, 2008 ³⁴	I/II	1 to 6	IH, Circ	0.25 mg/Kg	No	Before inuction	Midazolam	Remifentanil + Diclofenac	Diclofenac & Acetaminiphen	CHEOPS	Nurses, Diclofenac given as needed by pain	No
Darabi ME*, 2008 ³⁴	I/II	2 to 6	IH, Circ	0.25 mg/Kg	No	After induction	Midazolam	Remifentanil + Diclofenac	Diclofenac & Acetaminiphen	CHEOPS	Nurses, Diclofenac given as needed by pain	No
Aydin ON*, 2007 ¹⁹	I/II	5 to 15	Adenotonsilectomy	0.5 mg/Kg + 6 µg/Kg/mn	No	After induction & peroperative	Midazolam	No	Tramadol	VAS	Nurses, Tramadol given as needed by pain	No
Aydin ON**, 2007 ¹⁹	I/II	6 to 15	Adenotonsilectomy	0.16 mg/mn	No	Peroperative	Midazolam	No	Tramadol	VAS	Nurses, Tramadol given as needed by pain	No
Dal D, 2007 ²⁰	I/II	2 to 12	Adenotonsilectomy	0.5 mg/Kg	No	After induction	Midazolam	Fentanyl	Metamizol + Acetaminophen	OPS	Nurses, Metamizol given as needed by pain	Metoclopropamide
Da Conciecao MJ*, 2006 ²¹	I/II	5 to 7	Adenotonsilectomy	0.5 mg/ kg	No	After induction	No	Diclofenac	Acetaminophen + Morphine	Oucher scale	Nurses, Morphine given as needed by pain	Dexamethasone + Ondansetron
Da Conciecao MJ**, 2006 ²¹	I/II	6 to 7	Adenotonsilectomy	0.5 mg/ kg	No	End of surgery	No	Diclofenac	Acetaminophen + Morphine	Oucher scale	Nurses, Morphine given as needed by pain	Dexamethasone + Ondansetron
O-Flahery JE, 2003 ²²	I/II	3 to 12	Adenotonsilectomy	0.15 mg/ kg	No	After induction	No	Fentanyl	Fentanyl + Codeine+ Acetaminophen	OPS	Nurses, Codeine given as needed.	Dexamethasone
Elhakim M, 2003 ²³	I/II	4 to 12	Adenotonsilectomy	0.1 mg/Kg	No	Before induction	No	Fentanyl+ Diclofenac	Morphine (titration PACU) + Acetaminophen	CHEOPS, VAS	No rescue analgesia	No
Murray WB, 1987 ²⁴	I/II	4 to 13	Adenotonsilectomy	0.5 mg/Kg	No	After induction	Trimeprazine	No	Not Discribed	CHEOPS	Nurses, Analgesia given as needed by pain	Droperidol
Kararmaz A, 2004 ²⁵	I/II	3 to 6	Adenotonsilectomy	6 mg/Kg	No	Before induction	No	Fentanyl	Tramadol + Fentanyl (agitation)	OPS	Nurses, Tramadol given as needed by pain	Ondansetron
Umuroglu T, 2004 ²⁶	I/II	5 to 12	Adenotonsilectomy	0.5 mg/Kg + 10 µg/Kg/mn	No	After induction & peroperative	Midazolam	No	Pethidine + Acetaminophen	NRS, CHEOPS	Nurses, Pethidine given as needed by pain	No
Abu-Shahwan I, 2008 ²⁷	I/III	2 to 12	Adenotonsilectomy	0.25 mg/Kg	No	After induction	Midazolam	Acetaminophen, morphine	Morphine + Acetaminophen + Codeine	CHEOPS	Nurses, Morphine given as needed by pain	Dexamethasone + Ondansetron
Batra YK, 2007 ²⁸	I/II	6 to 15	Adenotonsilectomy	0.5 mg/ kg + 2 µg/Kg/mn	No	After induction & peroperative	Midazolam	remifentanil	Morphine: titration and PCA	CHEOPS, VAS	PCA, No rescue medication	No
Zahra FA, 2008 ³⁰	I	5 to 12	Adenotonsilectomy	1 mg/Kg	No	After induction	No	No	Ketorolac	VNS	Nurses, Ketorolac given as needed by pain	No
Bazin V, 2010 ³⁶	I/II	0.5 to 6	Ambulatory Surgeries	0.15 mg/ kg + 1.4 mg/Kg/h (24h)	No	After induction & postoperative	Midazolam	Caudal analgesia, Acetaminophen and Diclofenac	Nalbuphine, Acetaminophen, Diclofenac	CHEOPS	Nurses, Nalbuphine given as needed by pain	No
Inanoglu K, 2009 ³⁵	I/II	2 to 12	Adenotonsilectomy	0.5 mg/Kg	No	After induction	No	Fentanyl and acetaminophen	Fentanyl and Acetimophen	OPS	Nurses, Fentanyl given as needed by pain	Metoclopropamide
Tarkkila P, 2003 ²⁹	I/II	1 to 5	Adenotonsilectomy	0.7 mg/Kg	No	Before induction	No	Acetaminophen	Oxycodone	Not discribed	Nurses, Oxycodone given as needed by pain	No

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Table 1: Characteristics of included studies using systemic ketamine. (IH : Inguinal Hernia, Circ : Circumcision; PCA : Patient Controlled Analgesia, VAS: visual Analog Scale, VNS: Verbal Numeric Scale).

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For Peer Review

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Table 2 : Characteristics of included studies using local or topic ketamine.

Autors, years	ASA	Age	Ketamine	Ketamine S(+)	Duration of Surgery	Premedication	Intraoperative analgesia	Postoperative analgesia	Preventive antiemetics
Erhan OL, 2007 ³⁹	I/II	3 to 7	0.5 mg/Kg	No	End surgery	No	No	Tramadol + Ibuprofen	No
Honarmand A*, 2008 ³⁷	I/II	3 to 12	0.5 mg/Kg	No	After induction	Midazolam	Fentanyl	Pethidine	No
Honarmand A**, 2008 ³⁷	I/II	3 to 12	1 mg/Kg	No	After induction	Midazolam	Fentanyl	Pethidine	No
Dal D, 2007 ²⁰	I/II	2 to 12	0.5 mg/Kg	No	After induction End surgery	Midazolam	Fentanyl	Metamizol + Acetaminophen	Metoclopropamide
Canbay O, 2008 ³⁸	I/II	2 to 12	20 mg	No	End surgery (topical)	Midazolam	Fentanyl	Acetaminophen	Metoclopropamide

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Table 3: Characteristics of included studies using caudal ketamine. (IH : Inguinal Hernia, Circ : Circumcision; Orch : orchidopexia).

Auteur	ASA	Age	Chirurgie	Ketamine	Ketamine S+	Local anesthetics used	Timing	Premedication	Peroperative analgesia	Postoperative analgesia	Preventive antiemetics
Akbas M*, 2005 ⁴⁰	I/II	2 to 12	IH and Circ	0.5 mg/Kg	No	Bupivacaine 0.25%, 0,75 ml/Kg	After induction	Midazolam	Fentanyl	Acetaminophen	No
Akbas M**, 2005 ⁴⁰	I/II	2 to 12	IH and Circ	0.5 mg/Kg	No	Ropivacaine 0.2%, 0,75 ml/Kg	After induction	Midazolam	Fentanyl	Acetaminophen	No
De Negri, 2001 ⁴²	I	1 to 5	IH and Orch	0.5 mg/Kg	S-Ketamine	Ropivacaine 0.2 %, 1 ml/Kg	After induction	No	No	Acetaminophen + Codeine	No
Gunes Y, 2004 ⁴²	I/II	10 to 5	IH	0.5 mg/Kg	S-Ketamine	Ropivacaine 0.4 %, 0,5 mg/Kg	After induction	No	No	Acetaminophen	No
Kumar P, 2005 ⁴³	I/II	10 to 1	IH	0.5 mg/Kg	No	Bupivacaine 0.25%, 1 ml/Kg	After induction	No	Fentanyl	Acetaminophen	No
Lee HM, 2000 ⁴⁴	I/II	12 to 1	Circ	0.25 mg/Kg	No	Ropivacaine 0.2%, 1 ml/Kg	After induction	No	Fentanyl	Acetaminophen	No
Locatelli BG*, 2008 ⁴⁵	I/II	0 to 6	Urologic	0.5 mg/Kg	S-Ketamine	LevoBupivacaine 0.2%, 2 ml/Kg	After induction	Midazolam	Fentanyl	Codeine + Acetaminophen	No
Locatelli BG**, 2008 ⁴³	I/II	0 to 6	Urologic	0.5 mg/Kg	S-Ketamine	LevoBupivacaine 0.2%, 2 ml/Kg	After induction	Midazolam	Fentanyl	Codeine + Acetaminophen	No
Nafiu OO, 2007 ⁵²	I/II	2 to 8	IH	0.5 mg/Kg	No	Bupivacaine 0.125%, 1 ml/Kg	After induction	No	Fentanyl	Morphine + Acetaminophen	No
Ozbek H, 2002 ⁴⁶	I/II	1 to 9	IH	0.5 mg/Kg	No	Alfentanil 20 µg/Kg	After induction	No	No	Acetaminophen	No
Weber F, 2003 ⁴⁷	I/II	0 to 9	IH and Circ	0.5 mg/Kg	S-Ketamine	Bupivacaine 0.125%, 1 ml/Kg	After induction	Midazolam	No	Acetaminophen	No
Pan AK, 2005 ⁵¹	I	5 to 10	IH	0.5 mg/Kg	No	Bupivacaine 0.25%, 1 ml/Kg	After induction	No	No	Acetaminophen	No
Pathania J, 2003 ⁴⁸	I	3 to 12	IH	0.5 mg/Kg	No	Bupivacaine 0.25%, 1 ml/Kg	End of surgery	Promethazine	No	Acetaminophen	No
Choudhuri A, 2008 ⁴⁹	I/II	3 to 9	IH	0.5 mg/Kg	No	Bupivacaine 0.25%, 0,5 ml/Kg	After induction	No	Pethidine	Acetaminophen	No
Naguib M, 1991 ⁵⁰	I	4 to 9	IH	0.5 mg/Kg	No	Bupivacaine 0.25%, 1 ml/Kg	After induction	No	No	Acetaminophen	No

Table 4 : Subgroup analysis of the effects of surgeries, opioid analgesics and the administration regime on the analgesic efficacy of intravenous ketamine. Data are expressed as odds ratio (OR) or standard mean difference (SMD) with the 95 % confidence interval (CI), I², p for I². NP: not performed. Results in bold indicate significant effect of ketamine on the studied outcome.* indicate the use of a random effect model.

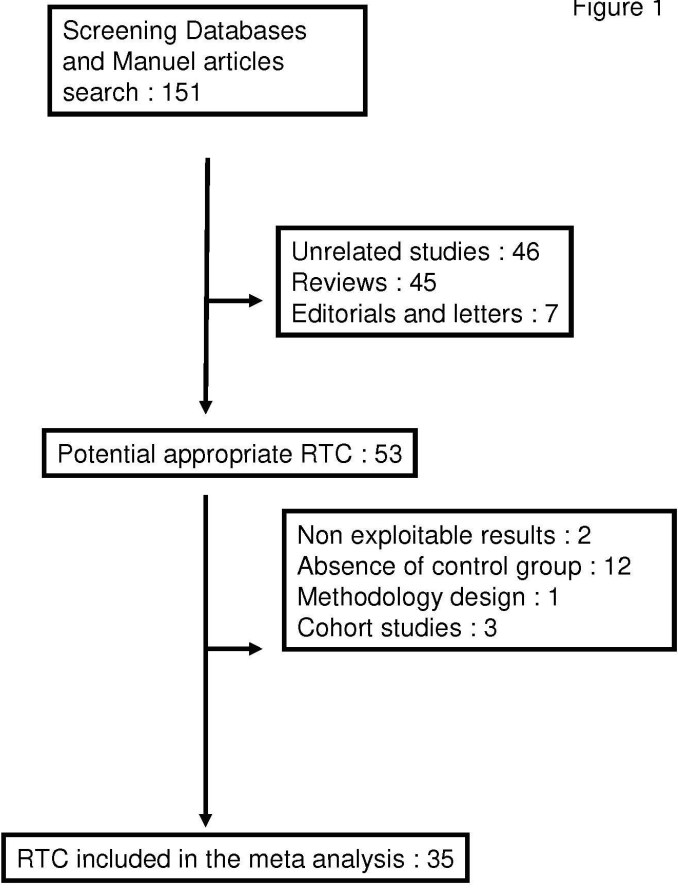
	PACU Pain (SMD)	Early pain (OR)	PACU analgesic administration (OR)	Early analgesic administration (OR)	Comments
Overall results	-0.45 [-0.73, -0.16], I ² = 68 %, p = 0.0003*	0.50 [0.25, 1.02], I ² = 78 %, p < 0.0001*	0.46 [0.29, 0.72], I ² = 0 %, P = 0.72	0.65 [0.35, 1.19], I ² = 75 %, p < 0.0001*	Ketamine improves pain management only in PACU.
Tonsillectomy	-0.98 [-1.60, -0.35], I ² = 73 %, p = 0.002*	0.15 [0.06, 0.35], I ² = 48 %, P = 0.08*	0.46 [0.29, 0.72], I ² = 0 %, P = 0.72	0.44 [0.20, 0.96], I ² = 70 %, p = 0.001*	Ketamine improves pain management pain in PACU and early postoperative period during tonsillectomy but not during other surgeries.
Abdominal / Urologic surgeries	-0.26 [-0.50, -0.02], I ² = 0 %, p = 0.9	0.66 [0.41, 1.07], I ² = 0 %, P = 0.7	No Study	1.23 [0.37, 4.05], I ² = 86 %, p < 0.0001	
Bolus	-0.69 [-1.11, -0.28], I ² = 77 %, p < 0.0001*	0.35 [0.16, 0.78], I ² = 79 %, P < 0.0001*	0.42 [0.26, 0.70], I ² = 0 %, P = 0.68	0.66 [0.28, 1.52], I ² = 79 %, P < 0.0001*	Bolus ketamine but not continuous administration improves pain management.
Bolus + Continuous	-0.06 [-1.47, 1.35], I ² = 0 %, p = 0.76	1.76 [0.83, 3.72], I ² = 0 %, p = 0.91	(one study)	0.50 [0.20, 1.22], I ² = 69 %, p = 0.007*	
Intraoperative opioids	-0.74 [-1.22, -0.26], I ² = 76 %, p < 0.0001*	0.57 [0.22, 1.47], I ² = 84 %, p < 0.0001*	0.39 [0.23, 0.66], I ² = 0 %, P = 0.71	1.27 [0.64, 2.52], I ² = 74 %, p = 0.003*	Ketamine improves early pain management when no opioid is given during the intraoperative period
No intraoperative opioids	-0.30 [-0.71, 0.10], I ² = 0 %, P = 0.63	0.54 [0.29, 0.99], I ² = 38 %, P = 0.18	0.78 [0.29, 2.10], I ² = 0 %, P = 0.8	0.23 [0.13, 0.40], I ² = 0 %, P = 0.63	
Postoperative opioids	NP	0.47 [0.130, 1.70], I ² = 86 %, P < 0.0001*	NP	0.95 [0.50, 1.79], I ² = 60 %, p = 0.01*	Ketamine improves early pain management when no opioid is given during the postoperative period.
No postoperative opioids	NP	0.56 [0.36, 0.88], I ² = 8 %, P = 0.36	NP	0.34 [0.11, 1.06], I ² = 83 %, P = 0.0001*	
intra and postoperative opioids	-0.74 [-1.22, -0.26], I ² = 76 %, p < 0.0001*	0.66 [0.15, 2.97], I ² = 89 %, p < 0.0001*	0.45 [0.28, 0.72], I ² = 0 %, P = 0.62	1.57 [1.01, 2.44], I ² = 10 %, P = 0.35	Ketamine improves early postoperative pain management when no opioid is given during the perioperative period.
No intra and no postoperative opioids	-0.30 [-0.71, 0.10], I ² = 0 %, P = 0.63	0.69 [0.36, 1.33], I ² = 22 %, P = 0.26	0.78 [0.29, 2.10], I ² = 0 %, P = 0.8	0.21 [0.10, 0.43], I ² = 0 %, P = 0.43	

Data are expressed as odds ratio (OR) or standard mean difference (SMD) with the 95 % confidence interval (CI), I², p for I². Results in bold indicate significant effect of ketamine on the studied outcome. * : indicate results computed using a random effect model.

	Duration of analgesia (SMD)	Analgesic consumptions at 24h (OR)
Overall	2.26 [1.53, 2.98] , I ² = 93 %, p < 0.00001*	0.26 [0.10, 0.66] , I ² = 85 %, p < 0.00001*
S+ Ketamine	2.35 [1.02, 3.67] , I ² = 95 %, p < 0.00001*	0.37 [0.10, 1.40], I ² = 84 %, p = 0.003*
Racemic	2.25 [1.34, 3.15] , I ² = 91 %, p < 0.00001*	0.21 [0.05, 0.82] , I ² = 86 %, p < 0.00001 *
Intraoperative Opioids	2.35 [1.52, 3.19] , I ² = 91 %, p < 0.00001*	0.36 [0.10, 1.29], I ² = 89 %, p < 0.00001*
No intraoperative Opioids	2.33 [0.92, 3.75] , I ² = 95 %, p < 0.00001*	0.15 [0.08, 0.31] , I ² = 0 %, p = 0.44*
Postoperative Opioids	3.50 [1.63, 5.37] , I ² = 91 %, p < 0.00001*	0.80 [0.27, 2.32], I ² = 68 %, p = 0.04*
No postoperative Opioids	2.03 [1.17, 2.88] , I ² = 92 %, p < 0.00001*	0.18 [0.05, 0.60] , I ² = 85 %, p < 0.00001*
Intra and/or Postoperative Opioids	3.07 [2.02, 4.12] , I ² = 94 %, p < 0.00001*	0.56 [0.19, 1.69], I ² = 83 %, p < 0.00001*
No intra and/or postoperative Opioids	1.05 [0.16, 1.93] , I ² = 89 %, p < 0.00001*	0.09 [0.04, 0.23] , I ² = 53 %, p = 0.08*

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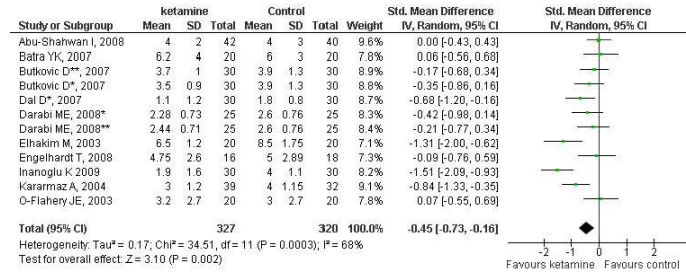
Figure 1



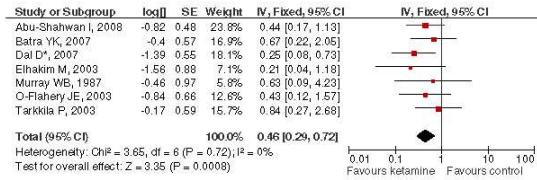
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Figure 2

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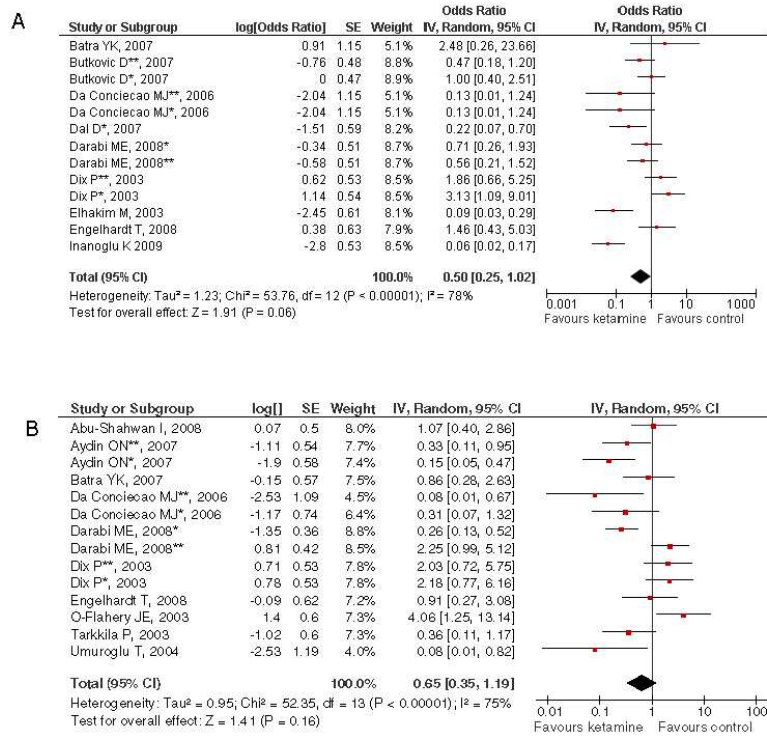
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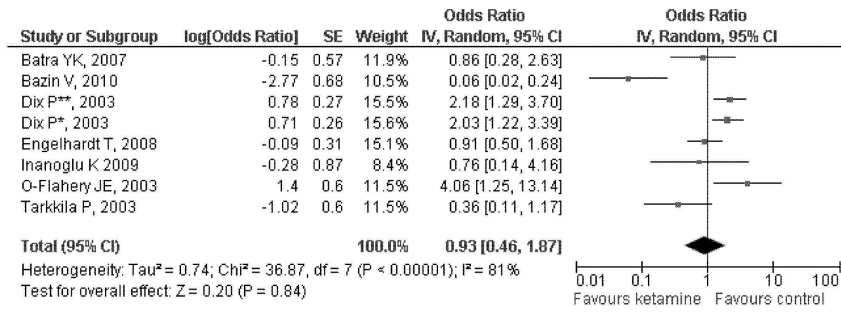
Review

Figure 3



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Figure 4



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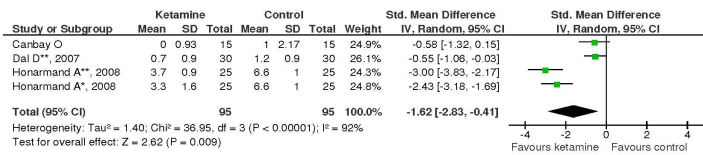
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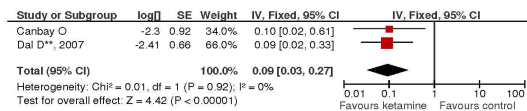
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Figure 5

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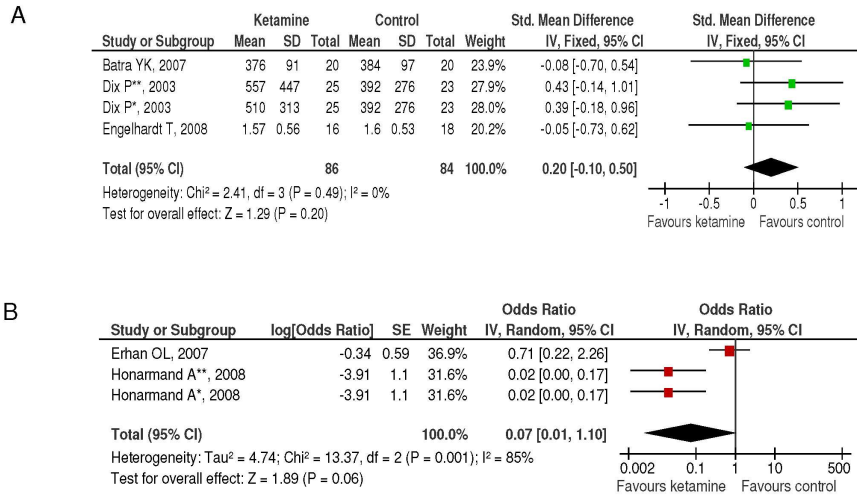
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Figure 6

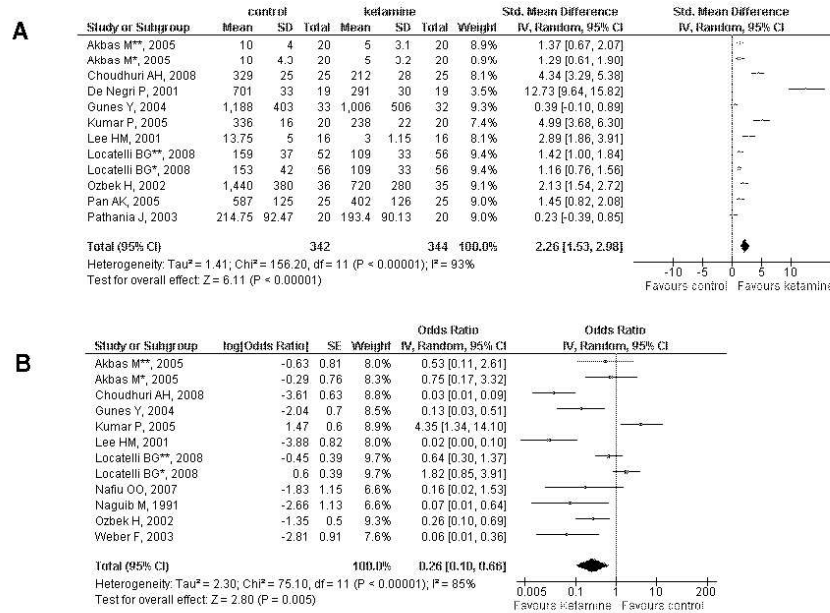


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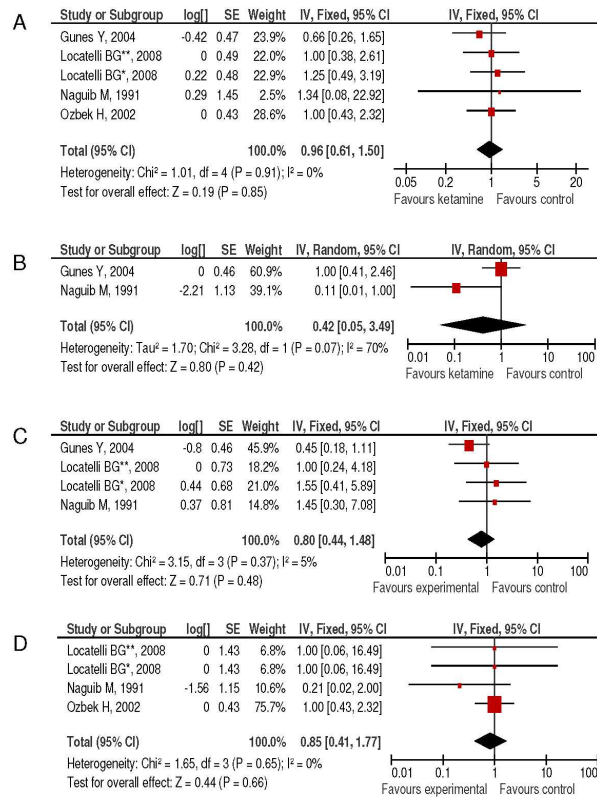
Figure 7



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Figure 8



209x297mm (200 x 200 DPI)