University of Alberta

The Role of Ketorolac and Intravenous Opioids in the Post-Operative Pediatric Patient: A Systematic Review

by

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in partial fulfillment of the requirements for the degree of

Master of Nursing

Faulty of Nursing

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Abstract

Managing post-operative pain in the pediatric population presents its own unique set of issues and concerns. Concern over the side effects and safety of opioids in the pediatric population can lead to a lack of adequate pain control. The purpose of this thesis is to examine the role of ketorolac (toradol), an intravenous non-steroidal anti-inflammatory, in the pain management of post-surgical pediatric patients.

The findings of this thesis research are presented in two manuscripts. The first manuscript contains a summary of the main findings of the systematic review and meta-analysis. The full systematic review is located in an appendix. Three main findings of the systematic review and meta-analysis are relevant. First, the belief that ketorolac poses a risk of post-operative bleeding is not supported. Second, ketorolac causes significantly less post-operative nausea and vomiting than the current gold standard of intravenous opioids. And third, ketorolac is found to be equivalent to intravenous opioids for mild to moderate pain, and as such is a reasonable alternative.

The topic of the second manuscript is finding evidence. It is written for nurse practitioners and deals with the approach to take to pose clear clinical questions. Sources for high quality systematic reviews are provided.

The discussion section of the thesis deals with the value of systematic reviews and meta-analysis. Research dealing with infrequent events and using small samples may produce biased results. A meta-analysis, which combines studies and increases sample size, will provide stronger evidence than single

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studies. They can guide practitioners to make informed decisions for their patients in an efficient and effective manner while avoiding small event size bias.

This research dealt with administration of drugs for pain. Many different methods of observing and recording pain scores are used in pediatrics. It would be beneficial for future research if pain scales were standardized so that systematic review and meta-analysis could be carried out more efficiently. A systematic review about the safety, side effects and benefits of oral ketorolac when used for pain caused by day surgery would also be valuable.

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Dedication

I would like to dedicate this thesis all of my family and friends who have supported me through out this process. Dr Janice Lander has been my inspiration for this project and any that may come in the future. She has repeatedly given me priceless advice and counseling to keep me on the right track. Dr Alex Clark and Dr Ramona Kearney who graciously agreed to sit on my thesis committee and have lent support and invaluable guidance in helping me complete this process.

To my parents whose unwavering belief that I can achieve greater things than I ever could have dreamed for myself, have made me who I am today academically, professionally and personally. There will never be enough words to thank-you.

To my amazing husband, Brett, and beautiful girls, Olivia and Mackenzie: Brett you are the corner stone of all things great in my life. Olivia, you have repeatedly taught me that small things can have great ripples of effect. And Mackenzie who has taught me that if you put your head down and charge forward, you can over come any obstacle.

Thank you all so very much.

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INTRODUCTION

A question that came up in my clinical practice was the stimulus for research reported in this thesis. Because one of our surgeons did not want to use opioids to manage post-operative pain in his pediatric patients, I looked for alternative drugs for moderate post-operative pain. This led me to look at the evidence relating to the use of intravenous non-steroidal anti-inflammatory drugs (NSAIDs). I came to the conclusion that a systematic review with meta-analysis was required and that it would provide important information for clinical decision-making.

The topic of my master's thesis is the role of intravenous ketorolac (toradol) in the management of post-operative pediatric patients. The findings of my research have been presented in the *mixed paper format* option accepted by the Faculty of Graduate Studies and Research of the University of Alberta. This format consists of two manuscripts to be submitted to journals for publication and an appendix containing the full systematic review written in the Cochrane style.

Background to the Research

Children often experience less than optimal pain management. Causes of inadequate pain control include hesitance about use of opioid analgesics, inability to provide analgesics in a timely manner, and failure to communicate evaluations of outcomes of pain treatments amongst staff (Dahl, 2002; Jacob & Puntillo, 2000; Rutledge, Donaldson, & Pravikoff, 2002).

Inadequate treatment of pain in children can have side effects involving the cardiovascular, respiratory, endocrine, metabolic, genitourinary,

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gastrointestinal, and immune systems (McCaffery & Pasero, 1999). Children may also manifest cognitive and behavioral problems as a direct side effect of uncontrolled pain (Kain et al., 2004 Dec)

Drugs referred to as NSAIDs have been available for some time in preparations that can be taken orally or rectally. More recently, NSAIDs have become available for intravenous use (ketorolac, marketed as Toradol™) NSAIDs act as non-selective inhibitors of the cyclooxygenase, inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. Cyclooxygenase catalyzes the formation of prostaglandins and thromboxane from arachidonic acid. Prostaglandins act as messenger molecules in the process of inflammation.

NSAIDs have a role in post-operative pain management for pediatric patients. NSAIDs may replace intravenous opioids altogether for the treatment of mild to moderate pain or be used in conjunction with opioid analgesics for severe pain. However, pediatric practitioners are concerned about a risk of post-operative bleeding with the use of intravenous NSAIDs and are reluctant to use them routinely. Concern about these side effects coupled with the lack of comprehensive research surrounding intravenous NSAIDs in the pediatric population have lead to variations in prescription and administration practices.

Researchers have investigated the role of ketorolac for the management of pediatric pain. Study methods vary in terms of dosage used, duration of treatment and route of administration. Gunter et al (1995) reported hat a single dose increased major post-operative bleeding enough to suggest that ketorolac

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is contraindicated in pediatric adenotonsillectomy patients. A systematic review and meta-analysis on the use of ketorolac following tonsillectomy was published in 2003 by Marret et al. their conclusion was that ketorolac not be used at all in any post-operative tonsillectomy patients. Concerns (Dsida, R. & Coté, C.J, 2004) have been raised over the quality of the Marret et al study and the method of data pooling used in their meta-analysis. Their search for studies for inclusion in the systematic review examined only two databases (MEDLINE and CCTR), excluded all non-english studies, and used a quality of study ranking system that eliminated studies thought to be of low quality. The seven studies included in their meta-analysis varied in methods and samples in significant ways: patient ages (adult and pediatric), route of administration (oral and parental), number or length of doses (one dose to two weeks of doses), and onset of NSAID treatment (upon completion of surgery to discharge home).

The evidence for use of intravenous ketorolac in pediatrics is not clear. Views about safety and efficacy of intravenous ketorolac are conflicting. No systematic review has been conducted to consider safety and efficacy of intravenous ketorolac for use across pediatric surgeries. A systematic review and meta-analysis is required to guide practice.

Objectives

Objective 1: To examine the side effects thought to be associated with the use of intravenous ketorolac in post-operative pediatric patients.

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Objective 2: To determine the benefits of intravenous ketorolac in the post-operative pediatric patients, including pain control and the reduction of side effects associated with intravenous opioids.

Objective 3: To inform nurse practitioners about formulating an effective clinical question and finding appropriate systematic reviews to support their clinical practice.

Manuscripts

My research led to the development of two manuscripts and a report of the full systematic review in the Cochrane format. As a mixed-paper format has been used, both of the manuscripts have been developed for submission for publication. Since the manuscripts are formatted for submission to different journals, their styles vary. It should be noted that the first manuscript summarizes a portion of the findings of the full systematic review. The focus of the full systematic review is on pain as a primary outcome. Manuscript one takes a different perspective and focuses on bleeding, and nausea and vomiting as primary outcomes to highlight the more novel findings. A flow chart illustrating the analyses presented in manuscript 1 can be found in Appendix A. The full systematic review can be found in Appendix B with flow charts summarizing the full analyses (located on pages 94 to 96).

In summary, the manuscripts consist of:

- a focused systematic review and meta-analysis (Manuscript I)
- information for nurse practitioners on forming clinical questions and locating high quality systematic reviews (Manuscript II)

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- A full systematic review and meta-analysis (Appendix B).

Each manuscript is briefly described below.

Manuscript One

The purpose of this paper was to summarize the methods of the systematic review and present the clinically relevant findings in a format that is suitable for publication in a medical journal. The three main conclusions of this paper are: 1) contrary to current belief, no greater risk of post-operative bleeding is associated with the use of intravenous ketorolac in the post-operative pediatric patient compared to opioids; 2) nausea and vomiting occurred significantly less in the intravenous ketorolac group than in the intravenous opioid group, and; 3) intravenous ketorolac and intravenous opioids provide similar post-operative pain control.

Manuscript Two

The second manuscript describes the need for nurse practitioners to become familiar with systematic reviews in order to provide the most up-to-date and relevant information to their patients. It illustrates the importance of and provides a method for formulating a clear clinical question when searching for quality research and information. The article provides practitioners with methods to locate systematic reviews from reputable sources and important clinical considerations when implementing the results of any systematic review.

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MANUSCRIPT ONE

RISKS AND BENEFITS OF INTRAVENOUS KETOROLAC IN POST-OPERATIVE PEDIATRIC PATIENTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Abstract

Context: The use of intravenous ketorolac in the management of pediatric post operative pain is controversial, primarily because of concerns about risk of post-operative bleeding.

Objective: To determine the effect of intravenous ketorolac on post-operative bleeding, nausea and vomiting and pain control in comparison with intravenous opioids in post-operative pediatric patients.

Data Sources: 31 databases, including published and unpublished literature with no language restrictions using the key words *opioids, narcotics, morphine/ or morphine derivatives, dilaudid, hydromorphone, meperidine, pethidine, demerol, fentanyl, ketorolac tromethamine, ketorolac, toradol; and associated drug reference numbers* references of retrieved articles; and direct author contact.

Study Selection: From 88 retrieved articles, 15 randomized controlled trials were identified, comprising 1022 post-operative pediatric patients requiring intravenous medications for pain control.

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Data Extraction: Data on post-operative bleeding, nausea and vomiting, pain scores, the need for "rescue" medication and time to discharge were extracted by two independent reviewers

Data Synthesis: Dichotomous data were analyzed and reported as a relative risk ratio (RR) with a 95% confidence interval. For analyses with significant heterogeneity (I^2< 50%), a random effects model was used as it is a more conservative estimate. Otherwise, a fixed effect model was used. Where small event rates occurred, Peto odds ratio was used with a fixed effects model. Continuous data were analyzed and reported as weighted means differences (WMD) where the units examined were similar. No significant difference in major post-operative bleeding events were found, however a decrease in milliliters of blood in post-operative drains was found in the ketorolac group (WMD= -3.20 ml; 95% CI -5.49 to -0.91). A significant decrease in the nausea and vomiting experienced by those who received ketorolac versus opioids was also found (RR,= 0.63; 95% CI, 0.51 to 0.77). Significantly less nausea and vomiting was also found in a subgroup analysis of strabismus repair patients (RR=28; 95% CI 0.15 to 0.53), day surgery patients (RR= 0.48; 95%; CI, 0.38 to 0.61), and those receiving high dose Ketorolac (≥ 0.6 mg/kg) (RR= 0.63, 95%CI 0.51 to 0.78). No significant difference was found in time to discharge from recovery room or hospital, or in the need for "rescue" medications.

Conclusions: Intravenous ketorolac is a safe and effective alternative to opioid therapy for post-surgical pediatric patients. The risks of post-operative

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bleeding commonly believed to be associated with ketorolac are not statistically supported. Any patient undergoing a surgery where post-operative emesis could be potentially detrimental to the surgical site should have ketorolac prescribed as a first line of defense for pain control as opposed to opioids.

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RISKS AND BENEFITS OF INTRAVENOUS KETOROLAC IN POST-OPERATIVE PEDIATRIC PATIENTS:

A SYSTEMATIC REVIEW AND META-ANALYSIS

Clinicians who are caring for children's post-operative pain may find a role for non-steroidal anti-inflammatory drugs (NSAID). These may be the drugs of choice when clinicians are concerned about side effects from opioids, such as respiratory depression, [1-5, 5-7] nausea and vomiting [1, 2, 4, 5, 8-14], decreased level of consciousness, ileus and urinary retention. [4, 10, 13] With the development of ketorolac, NSAIDs can now be administered intravenously. Ketorolac provides analgesic effects similar to opioids when used for mild to moderate pain. [1, 4, 9-12, 14, 16-19] It also has the added benefits of having anti-pyretic and anti-inflammatory properties, and an opioid sparring effect [20]. On the negative side, clinicians believe that intravenous NSAIDs increase risk of post-operative bleeding and many are hesitant to use it [12, 16, 18, 19, 21-24]. Studies of children undergoing tonsillectomy found that ketorolac increased the number of post-operative bleeding events [18], risk of a child experiencing a major bleeding episode [18] and bleeding time.[16] The results of these studies and a meta-analysis[25] of studies of pediatric tonsillectomy led to recommendations that ketorolac not be used in pediatric patients following tonsillectomy.

In 2003 Marret et al[25] conducted a systematic review, with meta-analysis, about use of ketorolac for post-tonsillectomy pain. They suggested that ketorolac not be used at all in any post-operative tonsillectomy patients because of the risk of bleeding. Concerns[31] have been raised over the quality of the review including

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the method of data pooling used in the meta-analysis. The literature search was not comprehensive and became more limited in scope when non-English publications were eliminated. Even more studies were removed when the quality ranking system eliminated those thought to be of low quality. The seven included studies varied significantly in important aspects of the methods. The studies varied in patient sampled (adult and pediatric), route of drug administration (oral and parental), number or length of doses (one dose to two weeks of doses) and onset of NSAID treatment.

In summary, safety and efficacy of intravenous ketorolac when used in pediatrics has not been established and we lack a systematic review that can guide practice. Our objective was to conduct a systematic review and meta-analysis to examine the risks and benefits of intravenous ketorolac for pediatric patients undergoing any surgical procedure.

METHODS

Study selection

Using the key words and Medical Subject Headings *opioids, narcotics, morphine/ or morphine derivatives, dilaudid, hydromorphone, meperidine, pethidine, demerol, fentanyl, ketorolac tromethamine, ketorolac, toradol,* and the associated drug reference numbers, we conducted a comprehensive literature search of 31 databases including: MEDLINE: (1966-January, 2006), PubMed: (1966 - January, 2006), EMBASE: (1988- January, 2006), and CINAHL: (1982-January, 2006). Selection criteria included: randomized controlled trials of pediatric patients less than18 years of age, who required intravenous pain

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medication immediately post-operatively; and a comparison of ketorolac with either an intravenous opioid or placebo. No language restrictions were imposed.

The initial search identified 1637 publications. A review of abstracts led to exclusion of 1564 of these publications for at least one of the following reasons: adult subjects (n=647), non-randomized controlled trial (n=503), non-human subjects (n=34), ketorolac used as an adjunctive medication (n=380). Eighty-eight full text articles were obtained and reviewed by two independent reviewers. An additional 73 studies were excluded from the review for the following reasons: non-randomized controlled trials (n=33), adult patients (n=16) and non-intravenous route of drug administration (n=23). One other study was excluded because the pediatric data could not be separated from the adult data [20]. Reference lists of the full text articles were examined to make certain that the search was complete. The authors were contacted and asked if they were aware of any published or unpublished articles on the topic of the systematic review. Figure 1-1 illustrates the selection and exclusion of studies for this systematic review.

Characteristics of Included Studies

The 15 studies [1-3, 8-12, 14, 18, 19, 26-29] included in this systematic review produced a sample of 1022 post-operative pediatric patients for analyses. None of the studies included patients less than 1 year of age. Where reported, the ASA status of patients was I or II.

Of the 15 included studies, seven compared intravenous ketorolac with intravenous opioids [2, 8, 10, 14, 18, 26, 28], five with placebo [11, 12, 19, 27, 29] and three with

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intravenous opioids and placebo [1, 3, 9]. In trials that employed a placebo, all subjects received analgesics, but not the study drugs. The placebos consisted of normal saline (in volumes that were identical to the study drugs).

Table 1-1 details the data collected in each of the studies. Data were collected in various studies on occurrence of post-operative bleeding, milliliters of blood loss, bleeding times, post-operative nausea and vomiting, time to discharge from recovery room or hospital, maladaptive behavior, need for administration of rescue doses or adjunctive medications and pain.

Methodological quality

All of the studies included in the review were described as randomized controlled trials. Thirteen of the studies had an allocation concealment that was unclear, making it difficult to ensure that the randomization was completely blinded [2,3,8-12,14,18,19,26-28]. Only two of the included studies had an allocation concealment method that was deemed adequate.[18,33]

Nine studies were considered to be of high quality when evaluated using a Jadad score ≥3. [1-3, 8,11,12,18,27,33] Only one study received a Jadad score of 4 [18]. Of the six low quality studies, four studies received a score of 2, [10,19,26,28] and two studies received a score of 1. [9, 14]

Data Extraction

Data were extracted by two reviewers (W.L.B. and J.L.). The reviewers worked independently to extract the data and then compared their results to identify any discrepancies. Discrepancies were resolved through discussion. Information extracted included study design, setting (inpatient vs. day surgery),

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drug comparisons, number and age of patients enrolled, number of patients completing trial, withdrawals or dropouts, blinding, co-interventions and type of surgery. The primary outcomes included post-operative bleeding (incidents of bleeding, milliliters of blood in drains, bleeding time and need for readmission because of bleeding); and any reported post-operative nausea and vomiting. Secondary outcomes included pain (any reported need for "rescue medications" or PRN medications, first reported pain scores, or observed pain), and time (in minutes) to discharge from recovery room and hospital.

While assessing the studies, reviewers extracted data to be used in the meta-analyses. Means and standard deviations were extracted when the data were continuous. If these measures were not reported, they were computed from graphs and figures, or calculated from ranges provided in the article. When dichotomous data were provided, the numbers of events were extracted. Eight studies included in this review were either missing some relevant data or published data in a form that could not be used. Although additional information was sought from all authors, no further data were obtained.

The reviewers also assessed quality of all included studies at the time of data extraction. All studies were examined for allocation concealment and given a Jadad score[32], which can be found on Table 1-1.

Statistical Analysis

All data were analyzed using a statistical package (RevMan 4.2.8)[30] provided by the Cochrane Collaboration. Dichotomous data were analyzed and reported as relative risk ratios (RR) with a 95% confidence interval and a fixed

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effects model. Where significant heterogeneity (I^2< 50%) occurred, a random effects model was used. Where small event rates occurred, Peto odds ratio was used with a fixed effects model. Continuous data were analyzed and reported as weighted means differences (WMD) where the units examined were combinable.

Where appropriate, subgroup analyses were completed. This included particular surgical procedures, day surgery versus inpatient surgery, high dose (>0.5/mg/kg/dose) versus low dose ketorolac (<0.5 mg/kg/dose), and study duration (>24 hours versus <24 hours).

RESULTS -

Post-Operative Bleeding

The occurrence of post-operative bleeding, as reported in eight studies,[2, 8-10, 14, 18, 28, 29] was not significantly different for use of ketorolac compared with opioids, regardless of the way that bleeding was measured. A number of comparisons were made. A separate (or subgroup) analysis was carried out with two studies where the surgery was tonsillectomy, and post-operative bleeding is a particular concern. [8, 18] No significant difference was found for ketorolac compared with opioids for reported occurrences of post-operative bleeding.

A single study [19] measured milliliters of post-operative blood loss in drains and bleeding time. The analysis of blood loss, which was statistically significant, favored the use of ketorolac over opioids (WMD, -3.20; 95% CI, -5.49 to -0.91). No statistical difference was found in mean bleeding time[2]. Analysis of the data from two studies looking at the need for re-operation or readmission to hospital due to bleeding found no difference between ketorolac and opioids [1, 18].

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The analysis also focused on the effect of the dose of ketorolac on bleeding. In comparing ketorolac and opioids, seven studies used high doses of ketorolac (>0.5/mg/kg/dose) [1, 2, 8, 9, 14, 18, 28] versus one study that used a low dose of ketorolac (<0.5 mg/kg/dose) [19]. No higher bleeding rates were found among those who received a high dose versus those who received a low dose.

The half life of ketorolac is approximately 2 hours, with it taking five to six drug half lives to deplete the anti-platelet effect [31]. This led to the question, will patients who have been on the drug for only a short amount of time have less bleeding events in the overall course of their treatment than those who have been administered the drug for a prolonged period of time. No difference was found for ketorolac and opioids for bleeding events and administration duration greater than 24 hours[19] versus less than 24 hours[1, 2, 8, 9, 14, 18, 28].

Five studies[1,9,12,27,29] compared ketorolac and placebo for any bleeding event post operatively. No significant difference was found. There was no statistical difference between placebo and ketorolac when examining intra-operative blood loss[12], patients requiring post-operative blood transfusions[29], readmission to hospital[1,12,29], day surgery[9] versus inpatients[1,12,27,29], high dose[1,9,12,29] versus low dose[27], and dose duration (>24 hours[27,29] versus <24 hours[1,9,12]).

Nausea and Vomiting

The occurrence of nausea and vomiting was recorded in 12 studies[1-3, 8-10, 12, 14, 18, 27-29], eight of which compared ketorolac and opioids. The meta-analysis determined a statistically significant decrease in nausea and vomiting when

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ketorolac was administered compared with opioids (RR, 0.53; 95% CI, 0.29 to 0.96). The number needed to treat (NNT) was 6.

It was possible to analyze certain surgical procedures where the occurrence of nausea and vomiting is a concern. An analysis of three studies [9, 10, 14] of strabismus repair surgery determined that nausea and vomiting occurred significantly less when ketorolac was used compared with opioids (RR=0.3; 95% CI 0.16 to 0.56, NNT=3). Nausea and vomiting was also occurred significantly less for tonsillectomy patients receiving ketorolac compared to opioids (RR=0.78; 95% CI 0.61 to 0.99; NNT=12). [8, 18]

Subgroup analyses of studies conducted with day surgery patients [8-10, 14, 18, 28] (RR=0.37; 95% CI 0.18 to 0.77, NNT=4), and of studies using high doses of ketorolac ≥ 0.6 mg/kg [1, 2, 8-10, 14, 18, 28] (RR=0.53, 95%CI 0.28 to 0.99, NNT=6) also found significantly less nausea and vomiting in the ketorolac group versus opioid comparison. No significant difference in occurrence of nausea and vomiting was found for ketorolac versus opioids in studies conducted in inpatient settings[1-3], and in studies where patients received low doses of ketorolac ≤ 0.5 mg/kg[3].

Time to Discharge

Three studies examined time to discharge from recovery room [1, 18, 28] and five examined time to discharge from hospital [9, 10, 18, 19, 28] No significant difference in discharge times was found for use of ketorolac versus opioids. Patients receiving ketorolac were discharged earlier from the recovery room compared with the placebo group [1, 10] (WMD -10.62; 95% CI -71.97 to -11.79), but not from the hospital [9, 29].

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Pain Control

An observational pain scale called the Objective Pain Scale was used by a number of researchers [1,8-10,14,28]. When examining the first reported pain score of all studies using the Objective Pain Scale, no significant difference was found in scores between those receiving ketorolac and those receiving opioids.

One measure of pain control is need for rescue medications. Patients receiving ketorolac did not require more "rescue" medications than those receiving opioids.[2, 3,9,10,14,18,28]. One study [29] examined patients who were receiving fentanyl in the recovery room for pain control. In addition to fentanyl, ketorolac was administered to one group of the study and a placebo to the other. The group receiving the ketorolac required significantly less fentanyl than the placebo counterpart (WMD -27.26; 95% CI -49.65 to -3.93).

COMMENT

This meta-analysis has produced three main findings that will be of interest to practitioners who work with post surgical pediatric patients. The first significant result is that ketorolac provides no greater risk of post-operative bleeding to patients than opioids or placebo comparisons. The second is that there is a significant reduction in nausea and vomiting in patients receiving ketorolac instead of opioids. And third is that pain control is comparable for ketorolac and opioids in mild to moderate pain.

Ketorolac has been thought to be associated with post-operative bleeding and its use avoided in pediatrics. It has been removed from use in the intra-operative formulary in the United Kingdom because of the risk of bleeding. This

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review and meta-analysis indicate that fears about bleeding with use of ketorolac are without foundation. While it is true that this meta-analyses indicated significantly greater loss of blood (as measured in a drain), the results cannot be considered to be conclusive. Only a single study with a small sample size (n=35 per group) was available for analysis.

The findings of several studies have caused a controversy about the potential for post-operative use of ketorolac to cause bleeding [18,25]. In fact, Gunter et al.[18] elected to stop their trial early due to concerns about bleeding caused by ketorolac. This is an example of a single study, with a low frequency event, having a larger impact on clinical behavior than may be warranted. Seemingly significant findings can be caused by a number of confounds (from design problems, to inadvertent biases, to statistical methods). One possibility here is surgical skill level as some of the procedures in the Gunter et al study were carried out by surgical residents. The approach for categorizing "major bleeding" may also have created problems. The major bleeding category only involved one patient requiring re-operation in the first 24 hours. The other 4 patients required further evaluation by medical staff, with one patient being discharged from the emergency room and three admitted to hospital. It would be interesting to learn if the patients who required readmission to the hospital for major bleeding had a significant drop in post-operative hemoglobin to correlate with the diagnosis. The re-operation for the subject in the ketorolac group came on post-operative day 5 which would be difficult to attribute to the drug itself as the anti-platelet effect does not last longer than 24 hours.

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Ketorolac causes less nausea and vomiting than opioids. Ketorolac should be considered for use particularly for surgical procedures where post-operative vomiting is a concern. It should also be used in day surgery so that parents can travel home without fear that the child will vomit during the trip.

Patients receiving ketorolac were found to have less pain, require less rescue medications, and a quicker discharge from recovery room, with no increase in negative side effects, than those receiving placebo. The opioid sparing effect of ketorolac should encourage practitioners to consider prescribing it as an adjuvant to intravenous opioids, where they would not have previously done so. Much debate has happened as to whether or not ketorolac causes a delay in bone healing in orthopedic patients. The current research examining this concern used animal models or adult patients. In the future, randomized control trials of pediatric patients need to be completed in order to resolve the issue.

This is a good example of clinical decisions being made on the basis of individual studies. Sometimes research with small sample sizes and infrequent events will produce results that do not stand up. A meta-analysis may help practitioners to make informed decisions for their patients in an efficient and effective manner while avoiding small event size bias.

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Figure 1-1. Summary of Article Selection Process

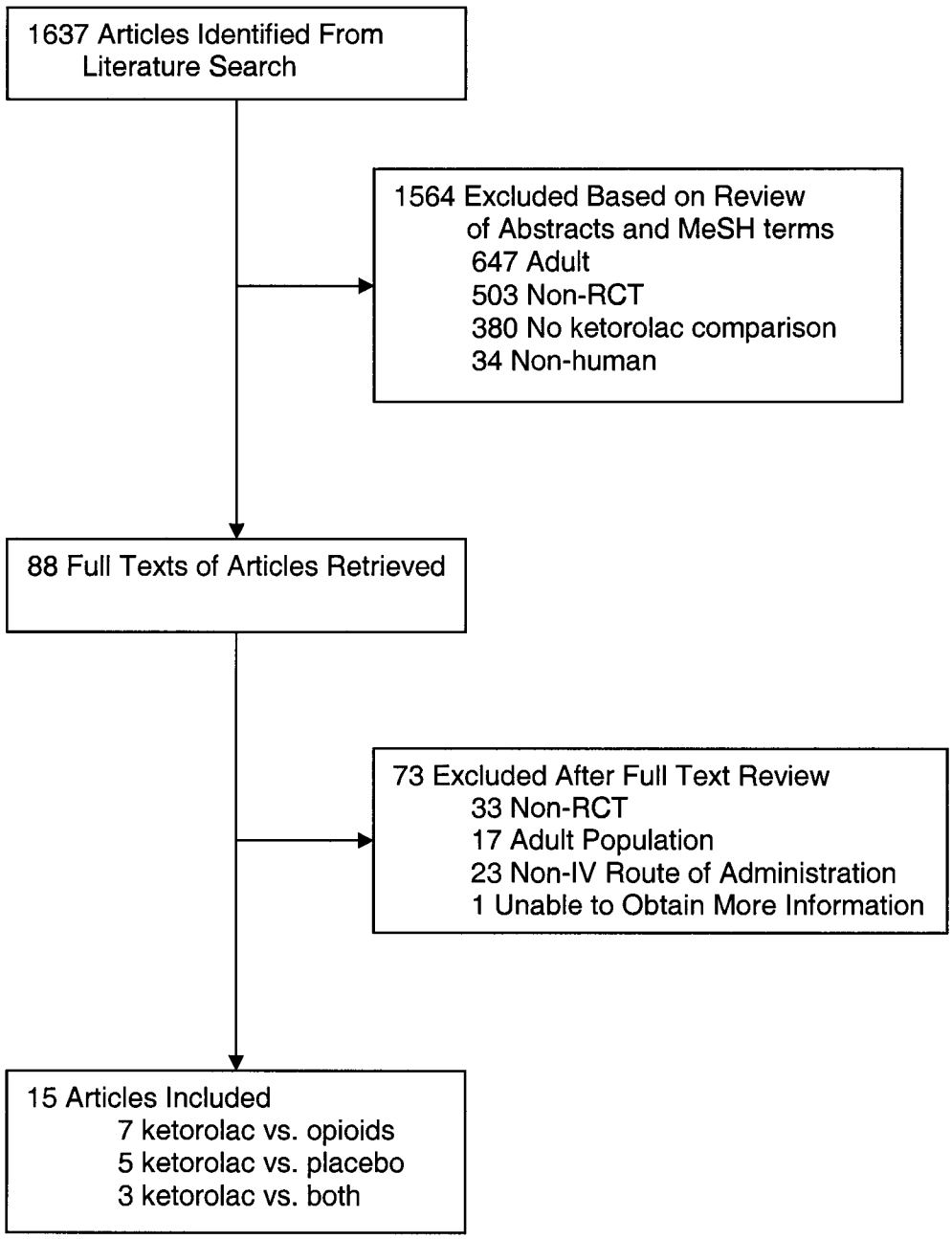

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Table 1-1. Characteristics of Randomized Controlled Trials Comparing Intravenous Ketorolac with Intravenous Opioid or Placebo

Source	Participants	Interventions	Statistical Information Used For Meta-Analysis						Jadad Score/ Allocation Concealment
			Pain	Bleeding	N&V	"Rescue" Meds	Time to Discharge	Maladaptive Behaviors	
Chiaretti, 1997[26]	• 52 patients • 1-10 yr • Inpatients	• Ketorolac 1.2 mg/kg q6h • Ketorolac 1.2 mg/kg (bolus) + 0.21 mg/kg/hr • Fentanyl 1 mcg/kg/hr • Fentanyl 1 mcg/kg/hr + Ketorolac 0.21 mg/kg/hr	✓	×	×	×	×	×	2/B
Gunter et al, 1995[18]	• 97 patients • 1-12 yr • Tonsillectomy • Day surgery	• Ketorolac 1mg/kg • Morphine 0.1 mg/kg	×	✓	✓	✓	✓	×	4/A
Gupta et al, 2005[19]	• 72 patients • 2 days to 18 yr • Surgery for congenital heart disease	• Ketorolac 0.5 mg/kg Q6h ATC • No ketorolac	×	×	×	×	✓	×	2/B
Keidan et al, 2004[8]	• 57 patients • 1.7 to 10 yr • Surgery: adenoidectomy and laser-assisted tonsillectomy	• Ketorolac 1 mg/kg • Fentanyl 2 μg/kg	×	✓	✓	×	×	✓	3/B
Lieh-Lai et al, 1999[2]	• 102 patients • 7-12 yr • Admitted to the intensive care unit post-operatively	• Ketorolac 0.6 mg/kg • Morphine 0.1 mg/kg	✓	✓	✓	✓	×	×	3/B
Maunuksela et al, 1992[3]	• 92 patients, • 3 to 12 yr • Elective surgery	• Morphine 0.1mg/kg • Ketorolac 0.2 mg/kg + 0.2 mg/kg, + 0.1 mg/kg • Ketorolac 0.5 mg/kg followed by 2 doses of placebo	×	×	×	✓	×	×	3/B
Mendel et al, 1995[9]	• 54 patients; • 1 to 10 yr • Strabismus surgery	• Ketorolac 0.9 mg/kg • Fentanyl 1 microgram/kg, • Saline placebo	✓	✓	✓	✓	✓	×	1/B

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Table 1-1. Characteristics of Randomized Controlled Trials Comparing Intravenous Ketorolac with Intravenous Opioid or Placebo Cont.

Munro et al, 1994[10]	• 42 patients, • 2-12 yr • Strabismus surgery	• Ketorolac 0.75 mg/kg • Morphine 0.1 mg/kg and metoclopramide 0.15 mg/kg IV	×	✓	✓	✓	✓	×	2/B
Munro et al, 2002[11]	• 35 patients, • 11-17 yr, • Posterior spinal fusion surgery	• Ketorolac 0.5 mg/kg • Normal Saline 5 ml	×	×	×	×	×	×	3/B
Park et al., 2000[27]	• 24 patients, • 4 to 11.5 yr, • Ureteral re-implantation surgery	• Ketorolac 0.5 mg/kg • Normal Saline	×	×	✓	×	×	×	3/B
Purday et al., 1996[28]	• 120 patients • 2-10 yr • Dental restorative surgery	• Ketorolac 0.75 mg/kg • Ketorolac 1.0 mg/kg • Ketorolac 1.5 mg/kg • Morphine 0.1 mg/kg IV	✓	✓	×	✓	✓	×	2/B
Romsing et al, 1998[12]	• 60 patients, • 5 to 15 yr • Tonsillectomy	• Ketorolac 1 mg/kg • Placebo	✓	×	✓	×	×	×	3/B
Shende et al, 1999[14]	• 52 patients • 2.5 to 15 yr • Strabismus surgery	• Ketorolac 0.9 mg/kg • Pethidine 0.5 mg/kg	✓	✓	×	✓	×	×	1/B
Sutters et al, 1999[29]	• 68 patients, • Avg 12.6 years of age, • Orthopedic surgery	• Ketorolac 1 mg/kg loading dose with 0.5 mg/kg q6h • Placebo	×	✓	✓	✓	×	×	3/A
Watcha et al, 1992[1]	• 95 patients • 5-15 yr	• Ketorolac 0.9 mg/kg • Morphine 0.1 mg/kg • Normal saline	✓	×	✓	×	✓	×	3/B

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Figure 1-2. Bleeding – Ketorolac vs. Opioids - Any Post-Operative Bleeding Event

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 10 Bleeding Events- Ketorolac vs Opioids
Outcome: 01 Any bleeding event

Study or sub-category	Ketorolac n/N	Opioids n/N	Peto OR 95% CI	Weight %	Peto OR 95% CI
01 All surgeries					
Watcha, 1992	0/32	0/31			Not estimable
Gunter, 1995	8/49	8/47		87.23	0.95 [0.33, 2.77]
Mendel et al, 1995	0/18	0/18			Not estimable
Purday et al, 1996	0/90	0/30			Not estimable
Lieh-Lai, 1999	0/54	0/48			Not estimable
Shende, 1999	0/26	0/26			Not estimable
Keidan et al, 2004	0/25	0/32			Not estimable
Gupta et al, 2005	1/35	1/35		12.77	1.00 [0.06, 16.32]
Subtotal (95% CI)	329	267		100.00	0.96 [0.35, 2.60]
Total events: 9 (Ketorolac), 9 (Opioids)					
Test for heterogeneity: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%					
Test for overall effect: Z = 0.08 (P = 0.93)					
02 Tonsillecotmy with/without adenoidectomy					
Gunter, 1995	8/49	8/47		100.00	0.95 [0.33, 2.77]
Keidan et al, 2004	0/25	0/32			Not estimable
Subtotal (95% CI)	74	79		100.00	0.95 [0.33, 2.77]
Total events: 8 (Ketorolac), 8 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.09 (P = 0.93)					
03 Strabismus repair					
Mendel et al, 1995	0/18	0/18			Not estimable
Shende, 1999	0/26	0/26			Not estimable
Subtotal (95% CI)	44	44			Not estimable
Total events: 0 (Ketorolac), 0 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
04 Cardiac surgery					
Gupta et al, 2005	1/35	1/35		100.00	1.00 [0.06, 16.32]
Subtotal (95% CI)	35	35		100.00	1.00 [0.06, 16.32]
Total events: 1 (Ketorolac), 1 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.00 (P = 1.00)					

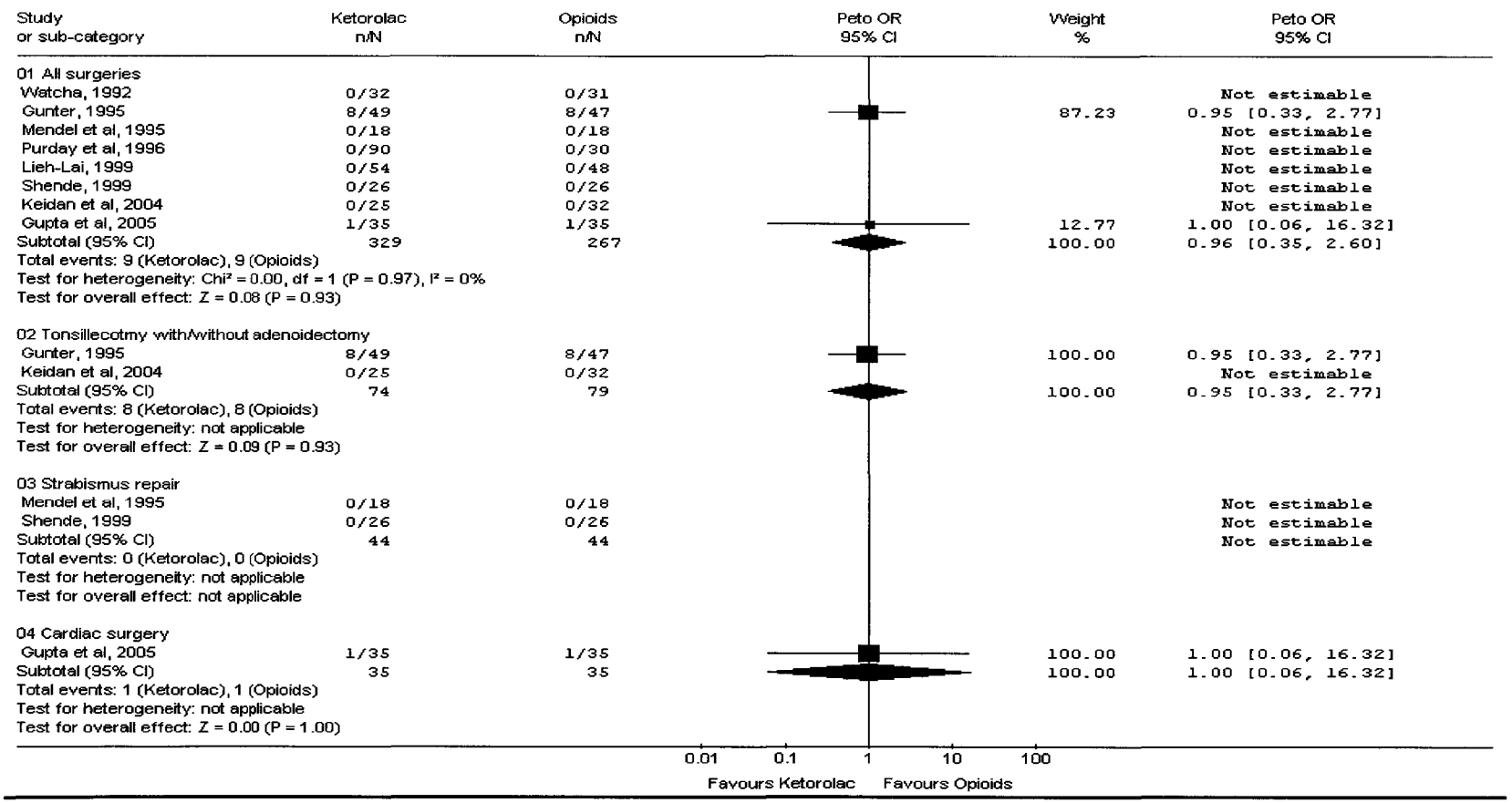

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Figure 1-3. Bleeding – Ketorolac vs. Opioids - Milliliters of Blood Loss in Drains

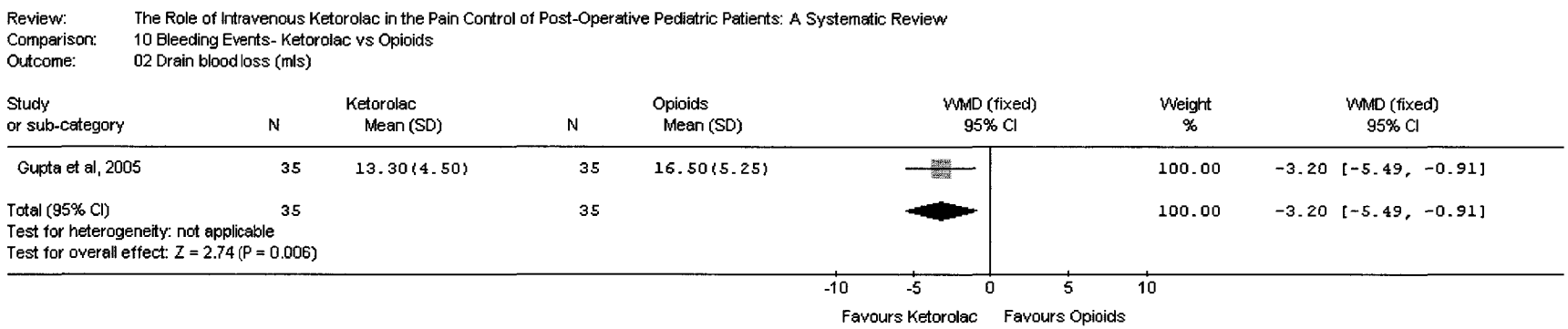

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Figure 1-4. Bleeding – Ketorolac vs. Opioids - Bleeding Time

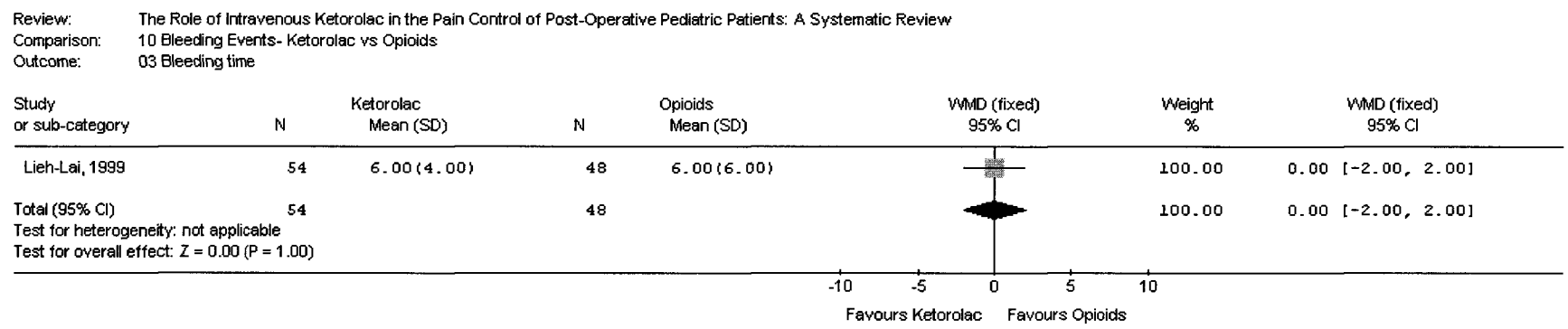

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Figure 1-5. Bleeding – Ketorolac vs. Opioids - Requiring Readmission to Hospital or Re-operation Due to Bleeding

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 10 Bleeding Events- Ketorolac vs Opioids
Outcome: 04 Readmission/Reoperation

Study or sub-category	Ketorolac n/N	Opioids n/N	Peto OR 95% CI	Weight %	Peto OR 95% CI
Watcha, 1992	0/32	0/31			Not estimable
Gunter, 1995	3/49	1/47		100.00	2.69 [0.37, 19.73]
Total (95% CI)	81	78		100.00	2.69 [0.37, 19.73]

Total events: 3 (Ketorolac), 1 (Opioids)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.97 (P = 0.33)

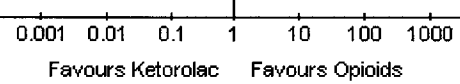

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Figure 1-6. Bleeding – Ketorolac vs. Opioids - Inpatients vs. Outpatients

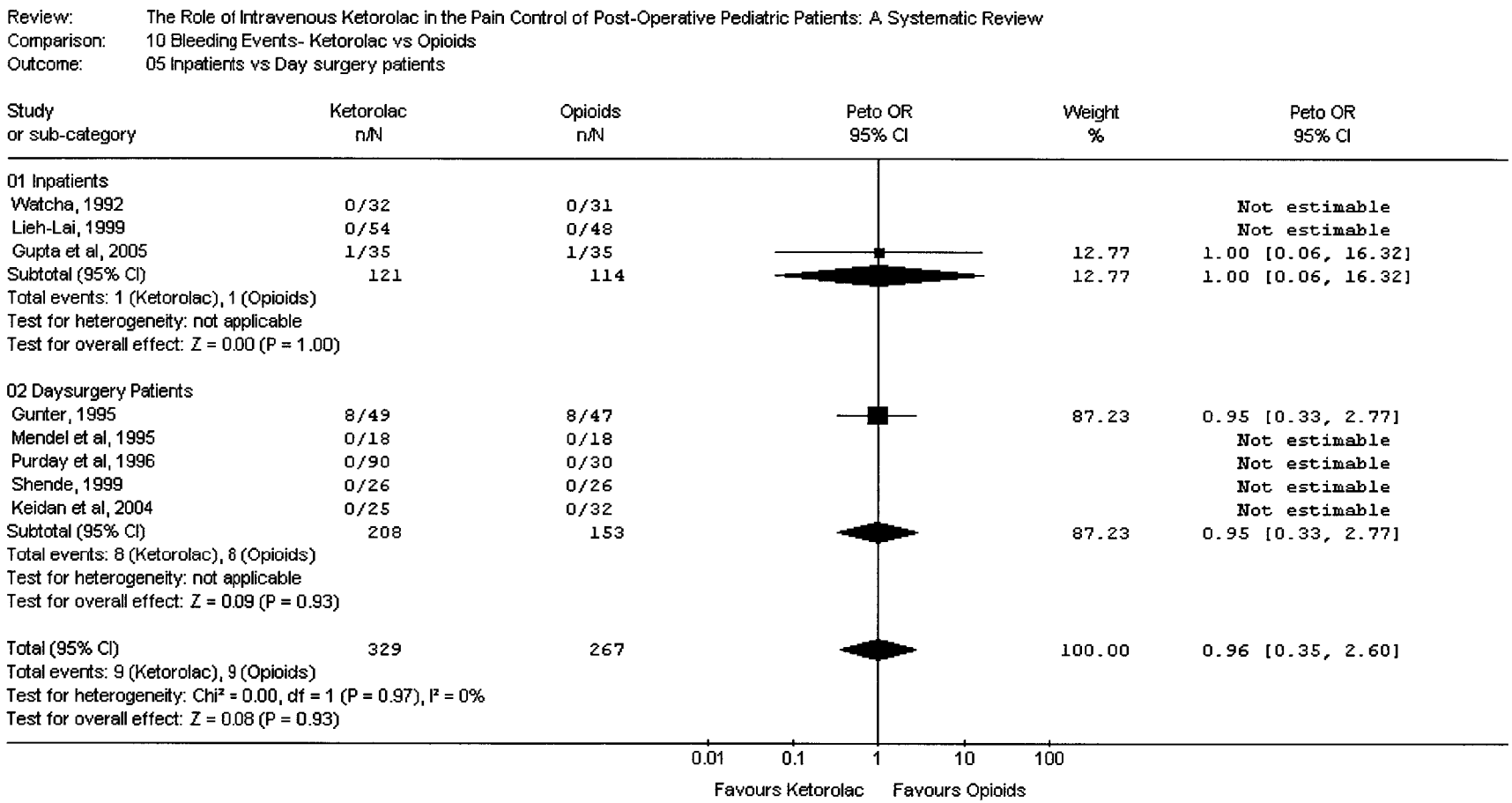

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Figure 1-7. Bleeding – Ketorolac vs. Opioids - High Dose Ketorolac vs. Low Dose Ketorolac

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 10 Bleeding Events- Ketorolac vs Opioids
Outcome: 06 High dose Ketorolac vs Low dose Ketorolac

Study or sub-category	Ketorolac n/N	Opioids n/N	Peto OR 95% CI	Weight %	Peto OR 95% CI
01 High dose Ketorolac (>=0.6 mg/kg/dose)					
Watcha, 1992	0/32	0/31			Not estimable
Gunter, 1995	8/49	8/47		87.23	0.95 [0.33, 2.77]
Mendel et al, 1995	0/18	0/18			Not estimable
Purday et al, 1996	0/90	0/30			Not estimable
Lieh-Lai, 1999	0/54	0/48			Not estimable
Shende, 1999	0/26	0/26			Not estimable
Keidan et al, 2004	0/25	0/32			Not estimable
Subtotal (95% CI)	294	232		87.23	0.95 [0.33, 2.77]
Total events: 8 (Ketorolac), 8 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.09 (P = 0.93)					
02 Low dose Ketorolac (<=0.5 mg/kg/dose)					
Gupta et al, 2005	1/35	1/35		12.77	1.00 [0.06, 16.32]
Subtotal (95% CI)	35	35		12.77	1.00 [0.06, 16.32]
Total events: 1 (Ketorolac), 1 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.00 (P = 1.00)					
Total (95% CI)	329	267		100.00	0.96 [0.35, 2.60]
Total events: 9 (Ketorolac), 9 (Opioids)					
Test for heterogeneity: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%					
Test for overall effect: Z = 0.08 (P = 0.93)					

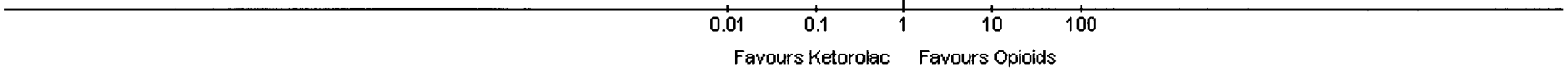

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Figure 1-8. Bleeding – Ketorolac vs. Opioids - Dose Duration >24 Hours vs. Dose Duration <24 Hours

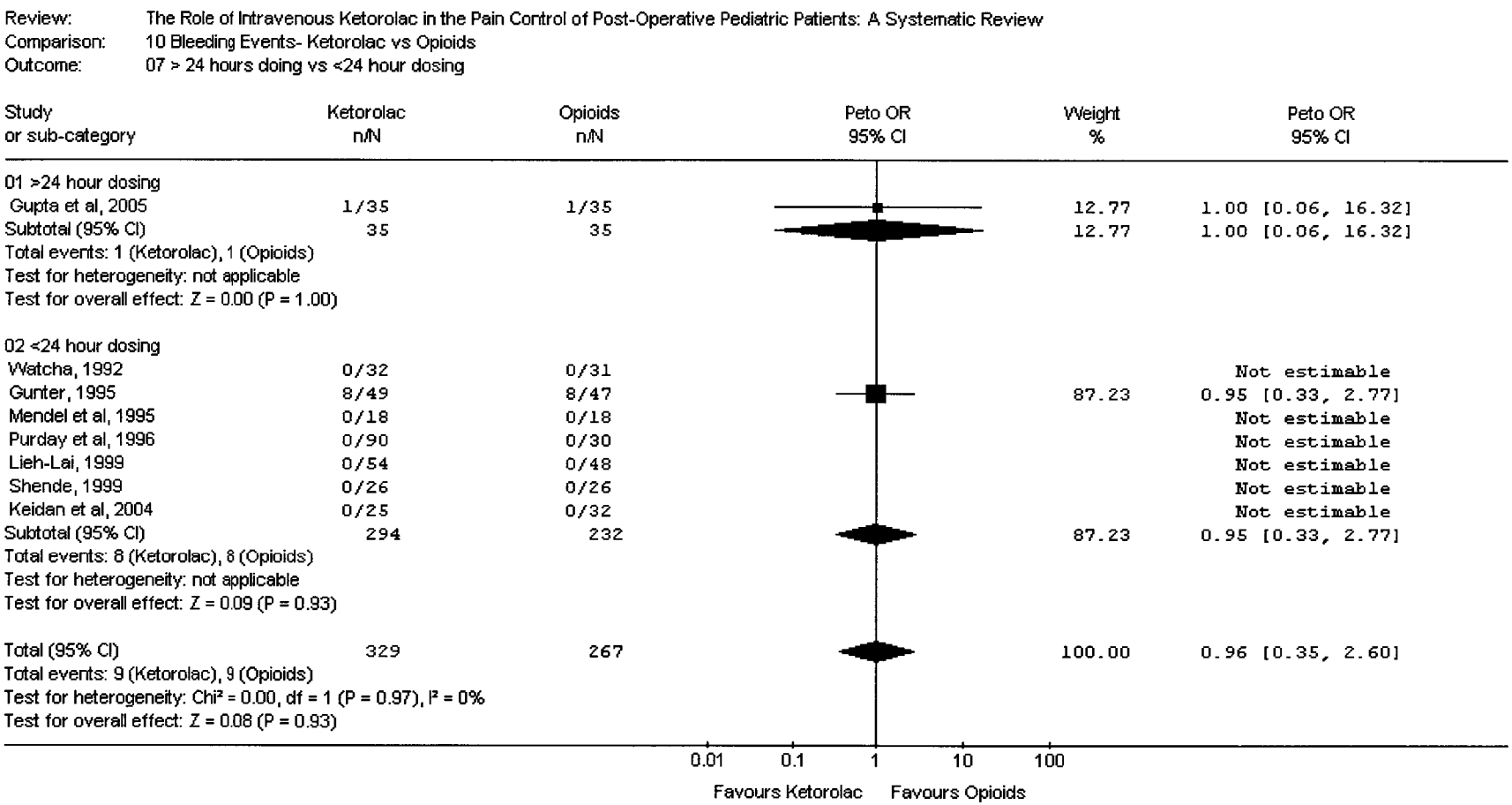

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Figure 1-9. Bleeding – Ketorolac vs. Placebo - Any Post-Operative Bleeding Event

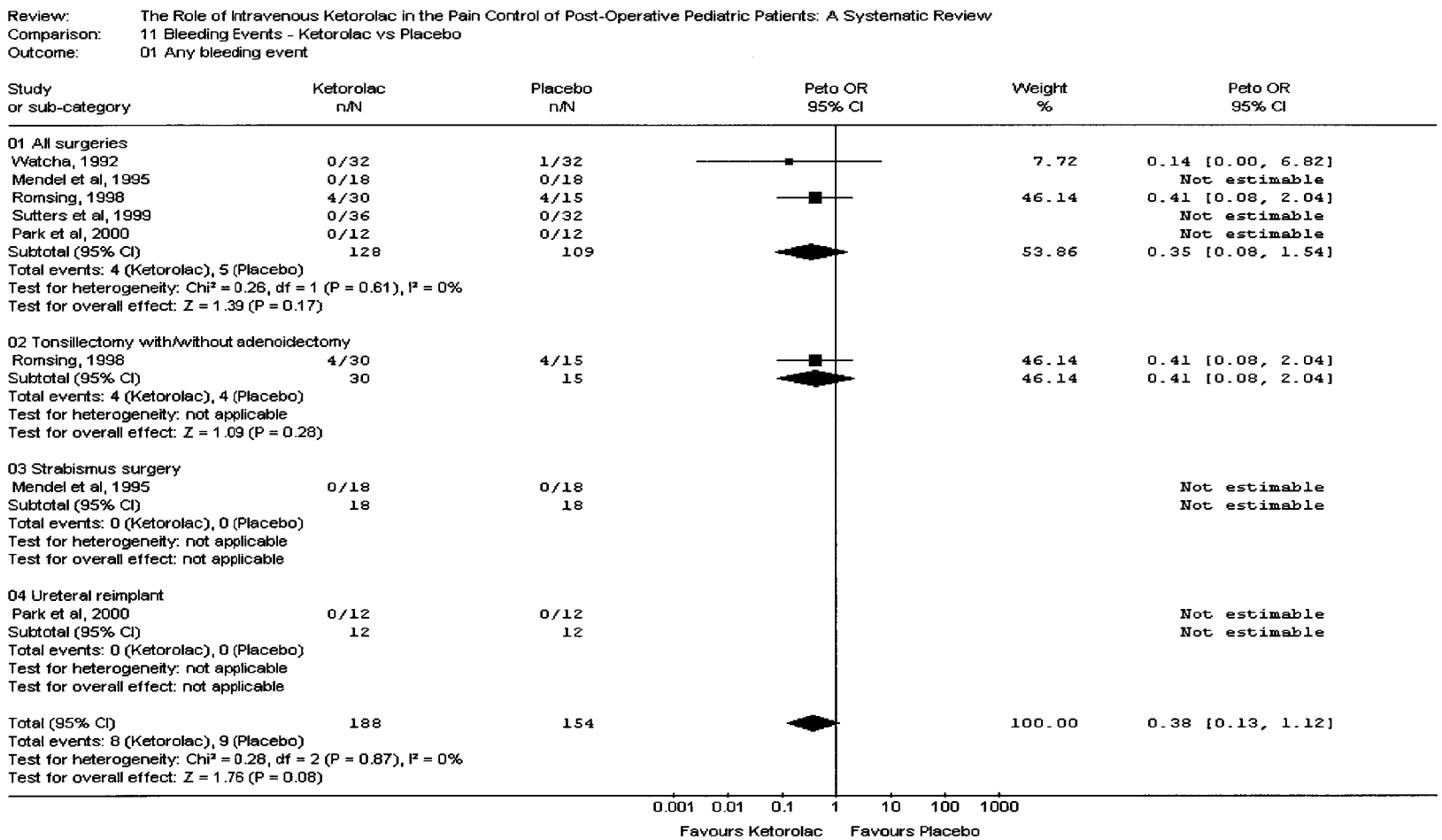

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Figure 1-10. Bleeding – Ketorolac vs. Placebo - Pre/Intra-operative Blood Loss

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 11 Bleeding Events - Ketorolac vs Placebo
Outcome: 02 Intraoperative blood loss

Study or sub-category	Ketorolac N	Ketorolac Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Romsing, 1998	40	3.15(2.50)	20	3.10(2.00)		100.00	0.05 [-1.12, 1.22]
Total (95% CI)	40		20			100.00	0.05 [-1.12, 1.22]

Test for heterogeneity: not applicable
Test for overall effect: Z = 0.08 (P = 0.93)

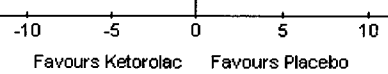

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Figure 1-11. Bleeding – Ketorolac vs. Placebo - Patients Requiring Post-Operative Blood Transfusions

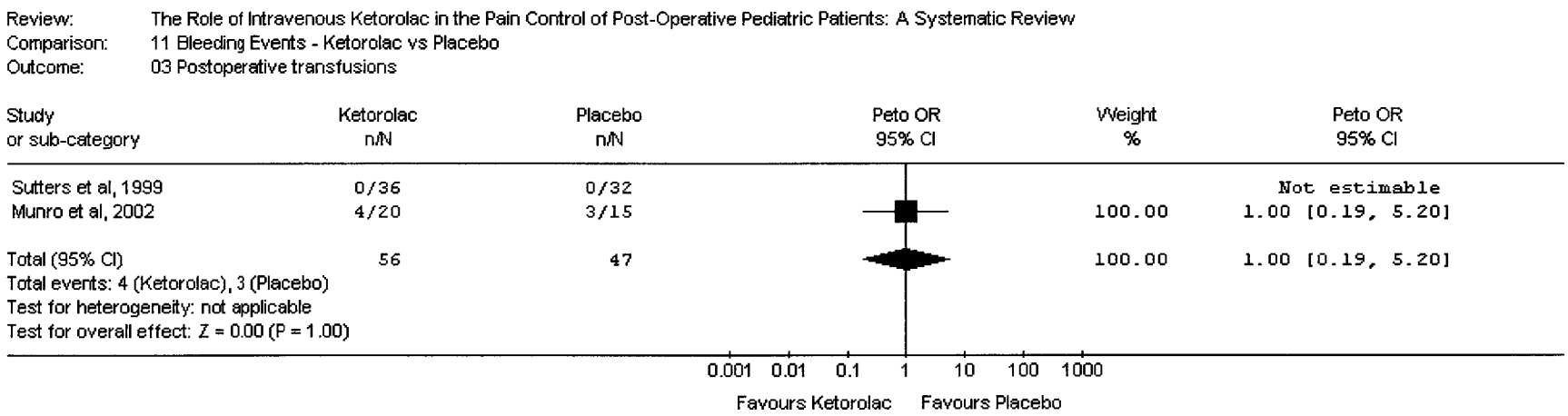

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Figure 1-12. Bleeding – Ketorolac vs. Placebo - Requiring Readmission to Hospital or Re-operation

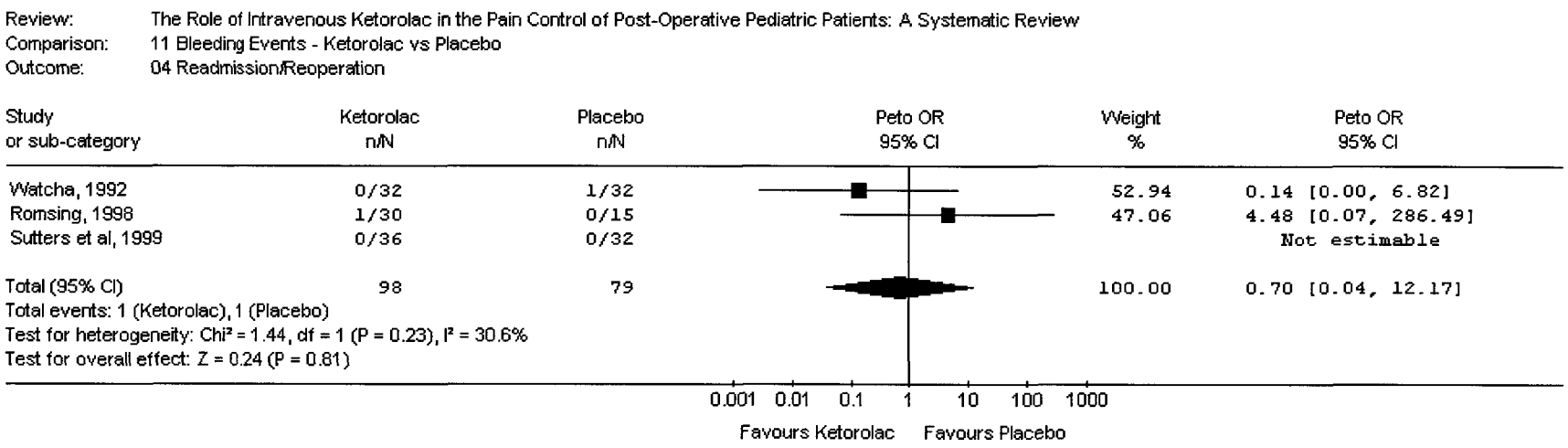

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Figure 1-13. Bleeding – Ketorolac vs. Placebo - Inpatients vs. Day Surgery

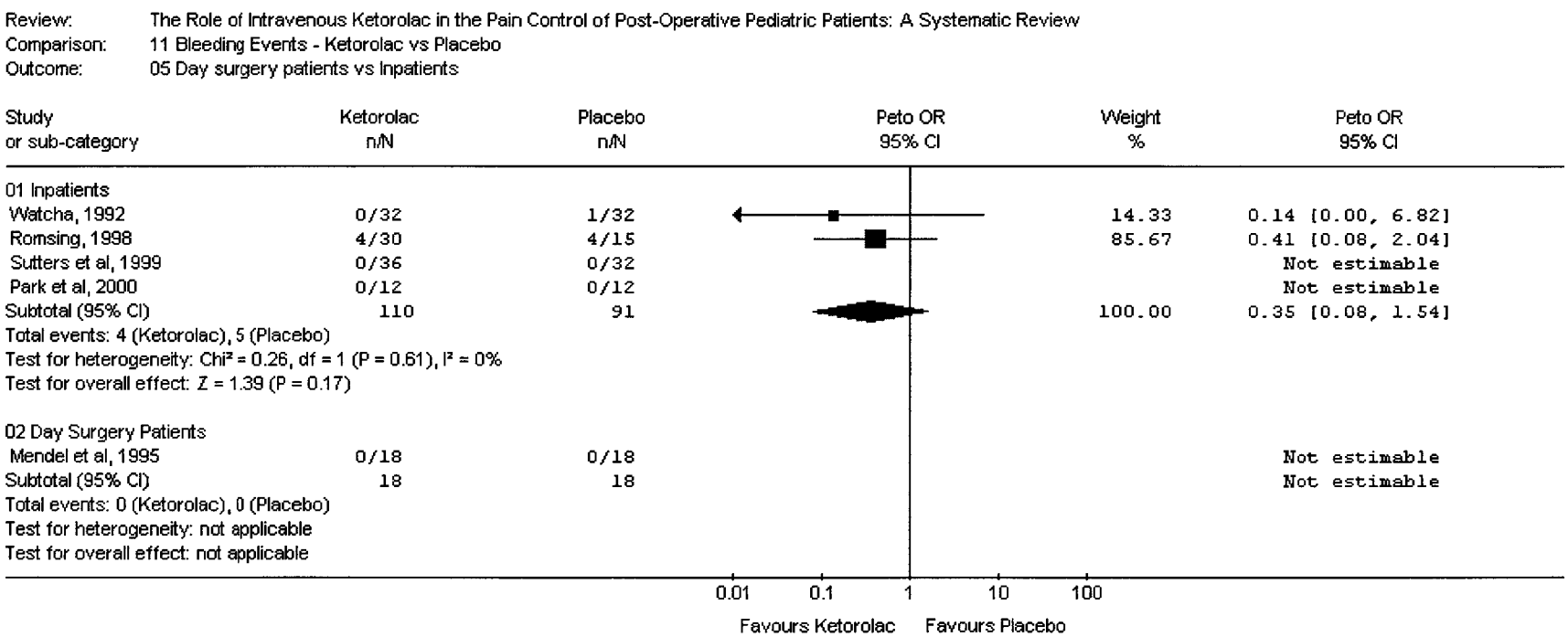

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Figure 1-14. Bleeding – Ketorolac vs. Placebo - High Dose (≥0.6 mg/kg/dose) Ketorolac vs. Low Dose (≤0.5 mg/kg/dose) Ketorolac

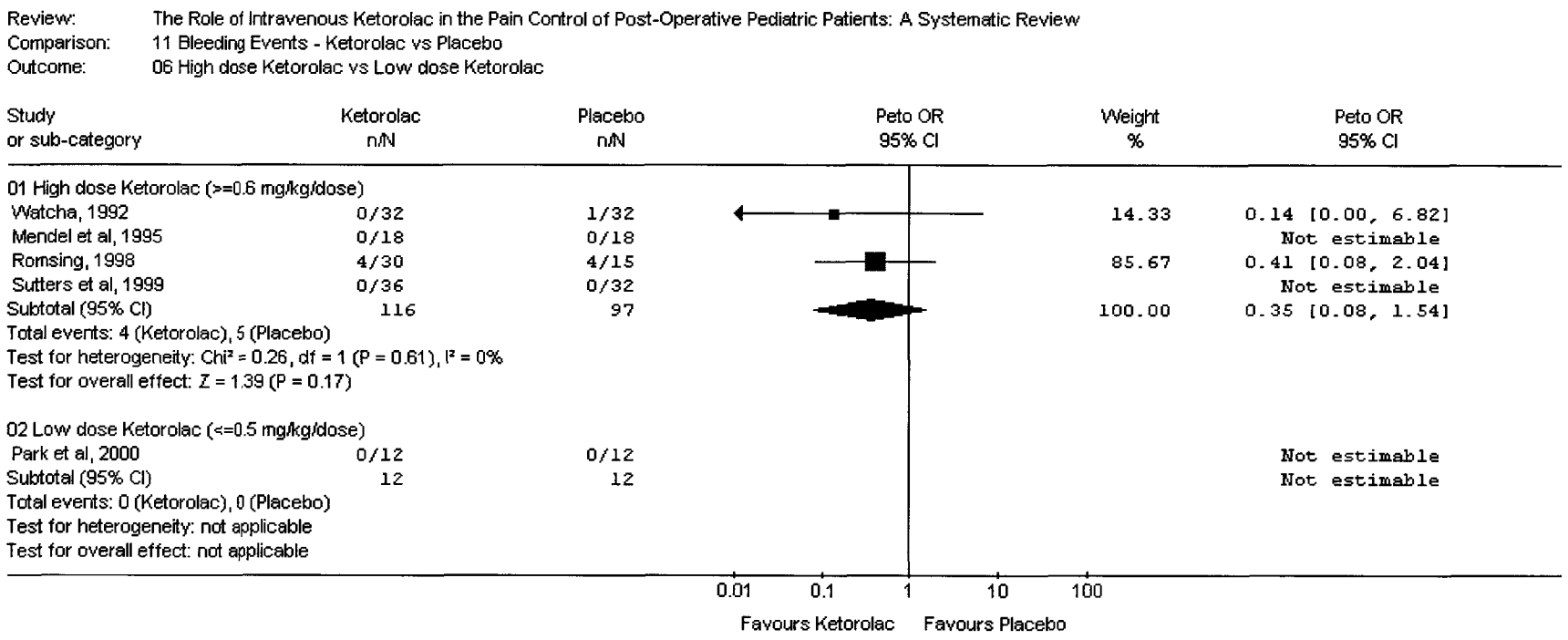

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Figure 1-15. Bleeding – Ketorolac vs. Placebo - Dose Duration >24 Hours vs. Dose Duration <24 Hours

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 11 Bleeding Events - Ketorolac vs Placebo
Outcome: 07 >24 hour dosing duration vs <24 hour dosing duration

Study or sub-category	Ketorolac n/N	Placebo n/N	Peto OR 95% CI	Weight %	Peto OR 95% CI
01 >24 hour dosing duration					
Sutters et al, 1999	0/36	0/32			Not estimable
Park et al, 2000	0/12	0/12			Not estimable
Subtotal (95% CI)	48	44			Not estimable
Total events: 0 (Ketorolac), 0 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
02 <24 hour dosing duration					
Watcha, 1992	0/32	1/32		14.33	0.14 [0.00, 6.82]
Mendel et al, 1995	0/18	0/18			Not estimable
Romsing, 1998	4/30	4/15		85.67	0.41 [0.08, 2.04]
Subtotal (95% CI)	80	65		100.00	0.35 [0.08, 1.54]
Total events: 4 (Ketorolac), 5 (Placebo)					
Test for heterogeneity: $Chi^2 = 0.26$, df = 1 (P = 0.61), $I^2 = 0\%$					
Test for overall effect: Z = 1.39 (P = 0.17)					

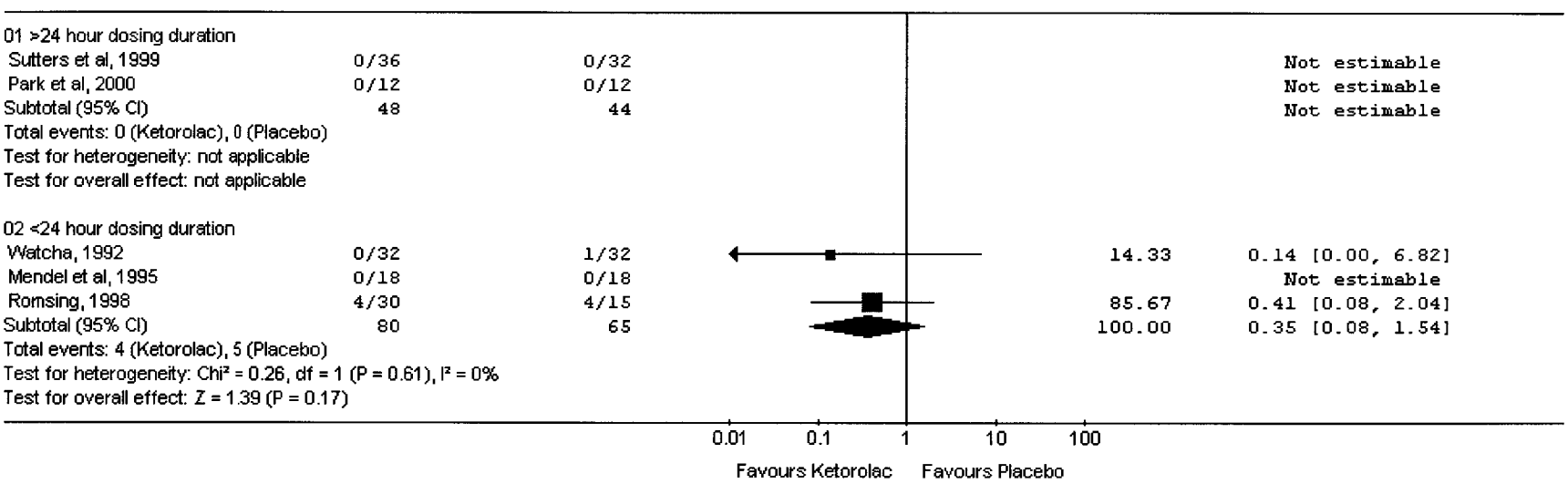

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Figure 1-16. Bleeding – Gunter et al Study

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 10 Bleeding Events- Ketorolac vs Opioids
Outcome: 08 Gunter et al Study

Study or sub-category	Ketorolac n/N	Opioids n/N	Peto OR 95% CI	Weight %	Peto OR 95% CI
01 Bleeding events <24 hours					
Gunter, 1995	13/49	2/47		100.00	5.32 [1.78, 15.93]
Subtotal (95% CI)	49	47		100.00	5.32 [1.78, 15.93]
Total events: 13 (Ketorolac), 2 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 2.99 (P = 0.003)					
02 Bleeding events >24 hours					
Gunter, 1995	7/49	12/47		100.00	0.50 [0.18, 1.35]
Subtotal (95% CI)	49	47		100.00	0.50 [0.18, 1.35]
Total events: 7 (Ketorolac), 12 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 1.38 (P = 0.17)					
03 Post-operative bleeding requiring re-operation					
Gunter, 1995	2/49	1/47		100.00	1.89 [0.19, 18.66]
Subtotal (95% CI)	49	47		100.00	1.89 [0.19, 18.66]
Total events: 2 (Ketorolac), 1 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.55 (P = 0.58)					
09 Any Bleeding					
Gunter, 1995	8/49	8/47		100.00	0.95 [0.33, 2.77]
Subtotal (95% CI)	49	47		100.00	0.95 [0.33, 2.77]
Total events: 8 (Ketorolac), 8 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.09 (P = 0.93)					
10 Major bleeding					
Gunter, 1995	6/49	5/47		100.00	1.17 [0.34, 4.08]
Subtotal (95% CI)	49	47		100.00	1.17 [0.34, 4.08]
Total events: 6 (Ketorolac), 5 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.25 (P = 0.81)					

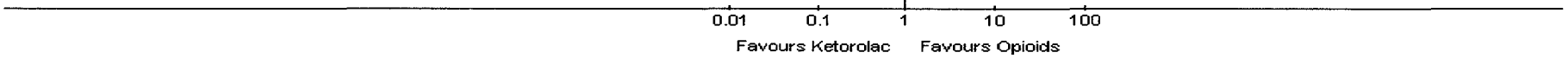

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Figure 1-17. Any Post Operative Nausea and Vomiting – Ketorolac vs. Opioids

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 08 N&V- Ketorolac vs Opioids
Outcome: 01 Had any N&V post-operativly

Study or sub-category	Ketorolac n/N	Opioids n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 All surgeries					
Maunuksela, 1992	2/61	2/31		4.96	0.51 [0.08, 3.44]
Watcha, 1992	8/32	18/31		15.66	0.43 [0.22, 0.84]
Munro et al, 1994	2/21	5/21		6.93	0.40 [0.09, 1.84]
Gunter, 1995	32/49	39/47		21.24	0.79 [0.62, 1.00]
Mendel et al, 1995	1/18	8/18		4.72	0.13 [0.02, 0.90]
Purday et al, 1996	12/90	16/30		16.32	0.25 [0.13, 0.47]
Lieh-Lai, 1999	22/54	4/48		11.52	4.89 [1.81, 13.18]
Shende, 1999	6/26	19/26		14.69	0.32 [0.15, 0.66]
Keidan et al, 2004	1/25	3/32		3.96	0.43 [0.05, 3.86]
Subtotal (95% CI)	376	284		100.00	0.53 [0.29, 0.96]
Total events: 86 (Ketorolac), 114 (Opioids)					
Test for heterogeneity: Chi² = 35.79, df = 8 (P < 0.0001), I² = 77.6%					
Test for overall effect: Z = 2.09 (P = 0.04)					
02 Tonsillectomy with/without adenoidectomy					
Gunter, 1995	32/49	39/47		84.30	0.79 [0.62, 1.00]
Keidan et al, 2004	1/25	3/32		15.70	0.43 [0.05, 3.86]
Subtotal (95% CI)	74	79		100.00	0.78 [0.61, 0.99]
Total events: 33 (Ketorolac), 42 (Opioids)					
Test for heterogeneity: Chi² = 0.32, df = 1 (P = 0.57), I² = 0%					
Test for overall effect: Z = 2.01 (P = 0.04)					
03 Strabismus repair					
Munro et al, 1994	2/21	5/21		26.30	0.40 [0.09, 1.84]
Mendel et al, 1995	1/18	8/18		17.92	0.13 [0.02, 0.90]
Shende, 1999	6/26	19/26		55.78	0.32 [0.15, 0.66]
Subtotal (95% CI)	65	65		100.00	0.30 [0.16, 0.56]
Total events: 9 (Ketorolac), 32 (Opioids)					
Test for heterogeneity: Chi² = 0.95, df = 2 (P = 0.62), I² = 0%					
Test for overall effect: Z = 3.75 (P = 0.0002)					

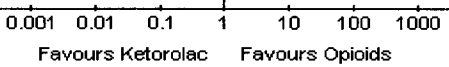

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Figure 1-18. Any Post Operative Nausea and Vomiting – Ketorolac vs. Opioids – Day Surgery vs. Inpatients

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 08 N&V- Ketorolac vs Opioids
Outcome: 02 Day surgery patients vs Inpatients

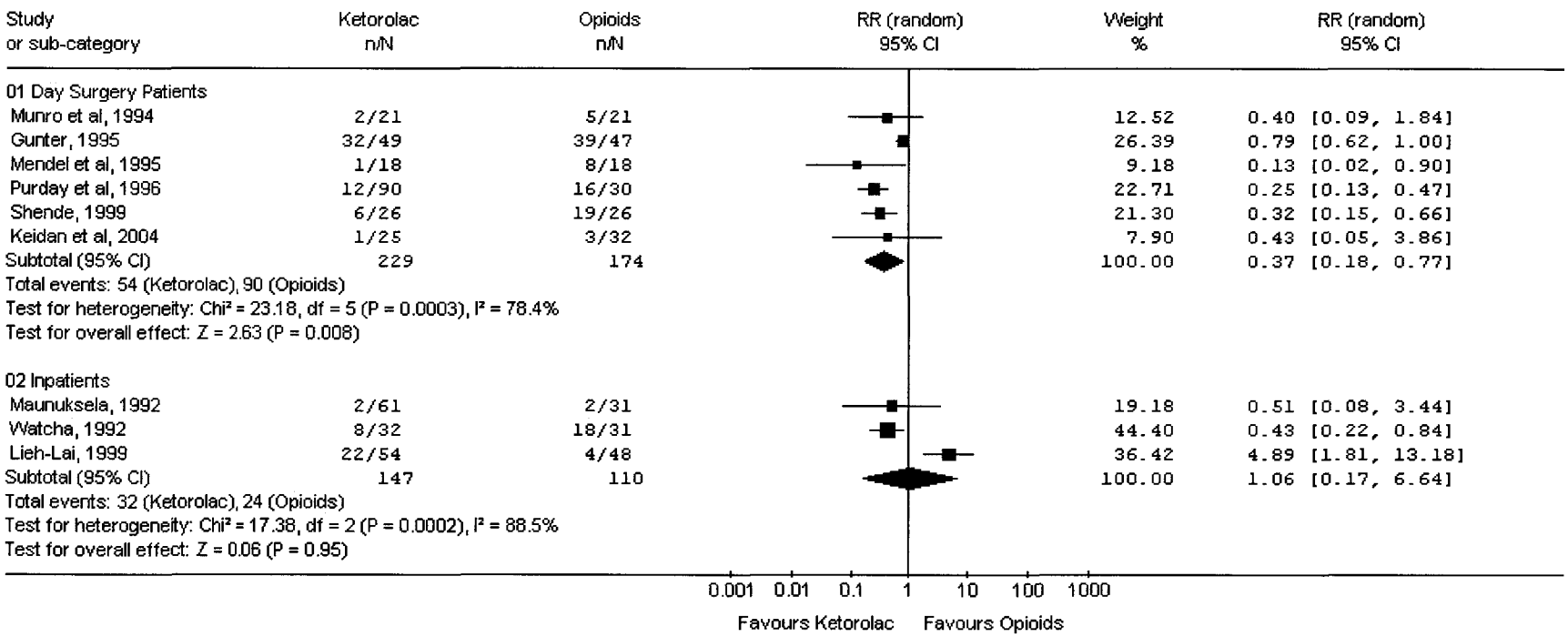

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Figure 1-19. Any Post Operative Nausea and Vomiting – Ketorolac vs. Opioids – High dose vs. Low dose ketorolac

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 08 N&V- Ketorolac vs Opioids
Outcome: 03 High dose Keotorlac vs Low dose Ketorolac

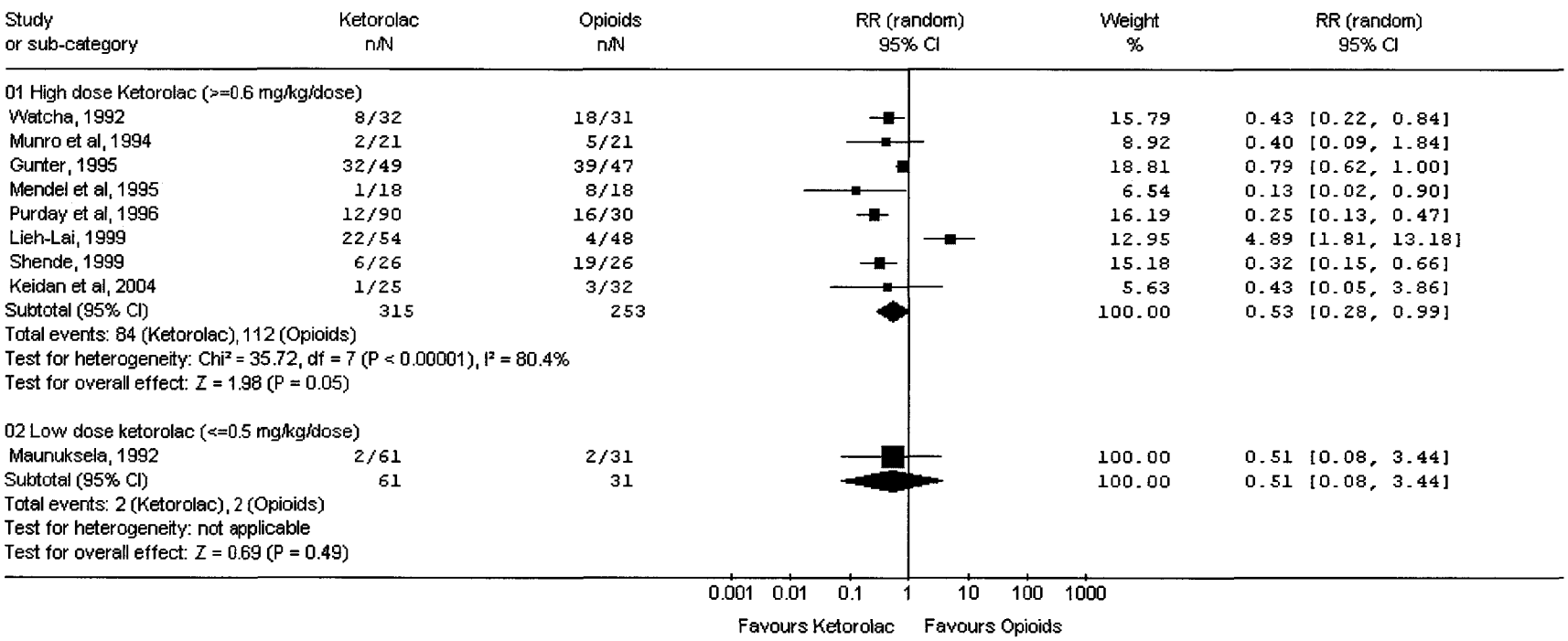

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Figure 1-20. Time (in minutes) to Discharge from Recovery Room (PARR) – Ketorolac vs. Placebo.

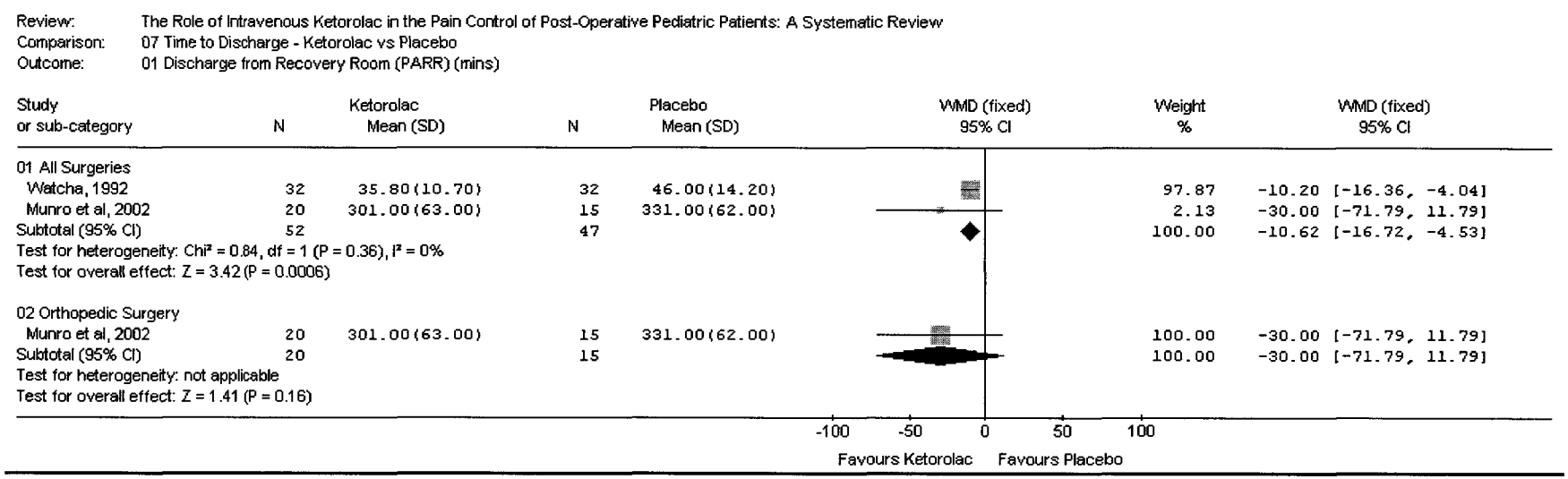

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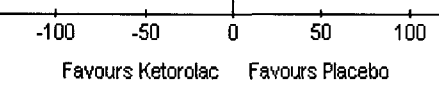
Figure 1-21. Rescue Dosing – Ketorolac vs. Placebo - Micrograms of Fentanyl Required in Recovery Room

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 05 Rescue Dosing - Ketorolac vs Placebo
Outcome: 02 Micrograms of fentanyl required for pain control in recovery room

Study or sub-category	N	Ketorolac Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Sutters et al, 1999	36	19.71(31.46)	32	46.50(58.95)		100.00	-26.79 [-49.65, -3.93]
Total (95% CI)	36		32			100.00	-26.79 [-49.65, -3.93]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 2.30 (P = 0.02)							



MANUSCRIPT TWO

SYSTEMATICALLY IMPROVING YOUR PRACTICE

Abstract

Aims: To help nurse practitioners ask a clear clinical question using the PICO method of question formulation; and to inform practitioners about sources of systematic reviews.

Background: No practitioner can keep up with the current volume of literature that is released by journals and the internet. When searching for literature pertinent to a clinical question, practitioners should rely more on summaries of the evidence such as systematic reviews.

Conclusions: Knowing how to ask clear questions and understanding about systematic reviews, how to locate them, and how to apply them to the clinical setting will allow practitioners to provide the best possible care to their patients in an effective and efficient manner.

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SYSTEMATICALLY IMPROVING YOUR PRACTICE

Introduction

Much has been said about evidence-based practice lately. Evidence based practice means that practitioners should be aware of current evidence and use it to provide care (Hamer & Collinson, 2005). The need for practice to be informed by evidence is essential for advanced nurse practitioners. The reality is that few nurse practitioners have time to search for and read thousands of articles, then pool the information and determine the implications for practice. This is where use of high quality filtered evidence should become an integral part of a nurse practitioners practice. By filtered we mean that a skilled researcher-clinician has evaluated the literature and prepared a summary. Reading a few summaries on a research topic is far more feasible than reading thousands of articles.

Although filtered evidence can take a several forms, an important one for nurse practitioners is the systematic review. High quality systematic reviews (SR) are designed to be a summary of all of the available literature on a topic. To prepare a SR, the researcher uses explicit methods that allow the authors to conduct an exhaustive search of the literature, critically appraise the findings, and synthesize the information into a clear and precise summary. Systematic reviews employ strict criteria to limit or eliminate bias and error that can be found in single studies and in studies about infrequent disease outcomes (Straus, Richardson, Glasziou, & Haynes, 2005). Quantitative reviews may include a meta-analysis, which is a combination of the statistical results from several

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different studies. SRs may also be carried out on qualitative studies and may include meta-synthesis, a method of combining qualitative study results (DiCenso, Guyatt, & Ciliska, 2005).

Asking the right clinical question

A key to providing evidence based healthcare is the ability to define a clear and succinct question (DiCenso et al., 2005). This allows practitioners to perform a precise literature search which will produce the most current literature on the subject. One method that is quick and easy to use is termed the "PICO" method of question development. PICO stands for "Population", "Intervention", "Control", and "Outcome." Population is defined as the people or participants of interest. Interventions are what treatment option is being considered and control refers to the comparison. Often the comparison would be the treatment that is considered the "gold standard" for the given situation. Outcome refers to what is hoped to be achieved by the intervention (i.e. remission, cure, pain control, etc.). By using the PICO method of question formation, not only is a clear question created, but the key or MeSH terms that should be used when conducting a search of the various databases are also identified. For example, imagine you have a 14 year old diabetic girl in clinic whose parents are asking about using the glycemic index for weight loss. You search for articles from 1996 to 2006 in MEDLINE, which is one database of health publications, using the terms "diabetes" and "diet." MEDLINE tells you that 8718 articles have been published on the topic of diabetes and diet. If the PICO method is used to create the clinical question, "adolescent diabetic patients" would be the population, "glycemic index

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diet" would be the intervention, no diet would be the comparison, and "weight loss" would be the desired outcome. Using the key words as MeSH terms, the results are significantly more manageable (2 publications on the topic). The PICO method is extremely useful when searching for SRs or for general searches when a SR is not available.

Finding systematic reviews

When looking for high quality systematic reviews, it is important that practitioners look for SRs that are peer reviewed and published by credible sources. Practitioners can locate high quality SRs online, depending on the resources subscribed to by their employers.

Cochrane Library

The Cochrane Library (www.cochrane.org) contains the Cochrane Database of Systematic Reviews (CDSR) which includes a regularly updated data base of completed systematic reviews as well as proposals for reviews to be completed in the near future. The Cochrane library also contains the Database of Abstracts of Reviews of Effectiveness (DARE), which are systematic reviews that are published outside of the Cochrane database.

CINAHL – Cumulative Index to Nursing and Allied Health

CINAHL provides medical information specifically for nursing and allied health. Access to CINAHL requires a subscription. You can search for relevant SRs by setting the limit on publication types to systematic reviews.

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MEDLINE

Many institutions have access to MEDLINE. Searches can be limited to SRs by selecting the "EBM Reviews" limitation.

Joanna Briggs Institute

The Joanna Briggs Institute (www.joannabriggs.edu.au) is affiliated with the University of Adelaide. The site offers easy to read summaries based on the results of systematic reviews. Some of the SRs are free of charge, and others require membership that can be purchased by individuals or institutions. SRs can be found on the website by selecting the "Members area" drop down menu, then "Educational" and "Systematic Reviews".

Sarah Cole Hirsh Institutes for Best Nursing Based on Evidence

The website (http://fpb.case.edu/HirshInstitute/reviews.shtm) contains systematic reviews that are focused specifically on nursing issues. The SRs are completed by faculty members and students and use nationally recognized experts to evaluate each systematic review.

National Quality Measures Clearinghouse

The National Quality Measures Clearinghouse (NQMC) is a web site for information on specific evidence-based health care quality measures and measure sets. NQMC (www.qualitymeasures.ahrq.gov) will allow you to access systematic reviews without requiring a membership. It is easy to use and can be searched by key terms or by treatment/intervention or disease/condition.

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Google

Google provides access to systematic reviews by adding "+ systematic review" to the subject. It results in a large number of hits that require some time to browse through, but it is accessible from any internet ready computer.

Incorporating systematic reviews into practice

If asking the right question and locating systematic reviews is half the battle of providing evidence based information to patients, applying the results in a clinical setting is the other half. Through compilation of various studies, systematic reviews provide a well rounded estimate of the true effects of a clinical intervention. With that being said, they are not always applicable to specific clinical situations, patient populations, or diagnosis. When deciding to implement the results of a systematic review into practice, it is imperative that the practitioner consider the following three issues, 1) Is the recommended treatment reasonable for the clinical setting, 2) Does this systematic review apply to this particular clinical situation/patient and 3) Does the recommendation fall in line with the patients values?

Reasonable for Clinical Setting

When considering the results of any systematic review, the practitioner must determine if the findings are reasonable, or even possible for the particular situation. For example, a northern nurse practitioner may be asking what to do for an infant whose head size is crossing percentiles. MRI is recommended. It would not be possible to have this done as the next step; however, it would be

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possible to make a referral to a center that has MRI capabilities to ensure that the child receives the best possible treatment.

Applicability to Individual Patients/Clinical Situation

It is not possible to find a systematic review that will perfectly match both patient and potential diagnosis for every clinical question. It is up to the practitioner to determine if the patient populations of the review or the diagnosis/treatment being considered are similar enough for the study to be relevant to the current situation. If the variations from the study to reality could potentially lead to the recommendations causing the patient harm it is the practitioners' responsibility to look for a more similar systematic review, or not implement the recommendations of the review.

Patient Values and Beliefs

Even with a systematic review that closely meets a clinical situation, and has clear statistically significant results, applying the results may not be in congruence with the patients' values and beliefs. In this situation it is important for practitioners to work with patients to ensure that they fully understand the recommendations that are being made and the literature that supports treatment recommendations. Patients should be aware of the potential risks and benefits of the recommended treatment. If the patient is well informed but the recommended course of action is against a closely held value or belief, then it is the practitioners' responsibility to explore other avenues of treatments that may be more acceptable to the patients needs.

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Conclusion

Systematic reviews are an invaluable tool for advanced nurse practitioners and their patients. With the rapid advances in medical treatment and technology, advanced nurse practitioners in all clinical settings must know how to develop a clinical question, and must have access to database that provides up-to-date and peer-reviewed systematic reviews. It is the practitioner's responsibility to be aware of where to find systematic reviews and when it is reasonable to apply them. Accessing systematic reviews will enable nurse practitioners to base their practice on research driven information, providing their patients with high quality information that will allow them to make the best possible decisions for themselves or their loved ones.

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References

DiCenso, A., Guyatt, G., & Ciliska, D. (2005). *Evidence based nursing : A guide to clinical practice*. St. Louis, Mo. ; London: Mosby.

Straus, S. E., Richardson, W. S., Glasziou, P., & Haynes, R. B. (2005). *Evidence-based medicine: How to practice and teach EBM* (3rd ed.). Toronto: Elsevier Churchill Livingstone.

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GENERAL DISCUSSION AND CONCLUSIONS

To conclude, each of the three objectives of this thesis project has been achieved. First, the risk of side effects associated with intravenous ketorolac was evaluated through the systematic review and meta-analysis. The results do not support the belief that intravenous ketorolac causes more post-operative bleeding events than intravenous opioids. These results require practitioners to reconsider excluding the drug from their formulary based on this unfounded belief. As well, incidence of post-operative nausea and vomiting was significantly less in the ketorolac group than in the opioid counterpart. Any patients who are undergoing surgery that may be compromised by post-operative emesis should be given intravenous ketorolac over intravenous opioids to protect the surgical site.

Second, the meta-analysis shows that intravenous ketorolac is equivalent to intravenous opioids for controlling mild to moderate post-operative pain in most situations. It is not clear why opioids out-perform ketorolac in day-surgery. This is a matter for further investigation. Outside of day-surgery, ketorolac could be a first line of defense against post-operative pain and less likely than opioids to cause nausea and vomiting.

The third objective was met by providing practitioners with quick and easy ways to formulate a clinical question, and find appropriate systematic reviews to meet their patient's clinical needs.

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Implications for Advanced Nurse Practitioners

Advanced nurse practitioners need to utilize systematic reviews as a way to assimilate the vast amount of literature that is available and updated on a frequent basis. Decisions for care should be based on all of the available literature, not just the most popular published trials. The basis for this systematic review is an excellent example of how a meta-analysis, especially when sample sizes are small, can lead to skewed results. In areas, such as pediatrics, where large event rates and large sample sizes do not happen often, research findings need to be pooled to come up with the best possible evidence for dealing with clinical problems.

The roles of advanced nurse practitioners are advancing at a rapid pace. As advance nurse practitioners break new ground, they need to ensure that they are doing so in an informed and educated manner. Developing clinical research skills in order to obtain and understand current research is essential to all practitioners' practices. Skills and resources need to be readily taught and available in all clinical settings in order to provide the best possible care to the public.

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APPENDICES

Page

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APPENDIX A - Summary of Meta-Analysis Findings

	Statistically Significant	Not Statistically Significant
Bleeding Events – ***Ketorolac vs. Opioids*** - *Any reported post-operative bleeding event*		
Any post-operative bleeding event		*
Tonsillectomy patients		*
Milliliters of blood loss in post-operative drains	**Favors Ketorolac** WMD=-3.20, 95% CI 5.49 to-0.91	
Post-operative bleeding times		*
Patients requiring re-admission/re-operation due to bleeding		*
High dose versus low dose ketorolac		*
Dose duration <24 hours versus >24 hours		*
Nausea and Vomiting – *Ketorolac vs. Opioids* -*Any reported post-operative nausea and vomiting*		
Any post-operative nausea and vomiting	**Favors Ketorolac** RR=0.63, 95% CI 0.51 to 0.77 NNT=5.79	
Strabismus repair patients	Favors Ketorolac RR=0.28, 95% CI 0.15 to 0.53 NNT=2.83	
Tonsillectomy patients		*
Day surgery patients	**Favors Ketorolac** RR=0.48, 95% CI 0.38 to 0.61 NNT=3.55	
High dose ketorolac	**Favors Ketorolac** RR=0.63, 95& CI 0.51 to 0.78 NNT=5.68	
Inpatients		*
Low dose ketorolac		*
Time to Discharge – *Ketorolac vs. Opioids* - *In minutes*		
Discharge from recovery room or PARR		*
Discharge from hospital		*
Ketorolac vs Placebo – In minutes		*
Discharge from recovery room or PARR	**Favors Ketorolac** WMD=-10.62, 95% CI -71.97 to -11.79	
Pain Scores – *Ketorolac vs. Opioids* -*First reported pain scores*		
Objective pain scale		*
Day surgery patients	**Favors Opioids** WMD=0.63, 95% CI 0.16 to 1.10	*

APPENDIX A - Summary of Meta-Analysis Findings Cont.

	Statistically Significant	Not Statistically Significant
Rescue Dosing – *Ketorolac vs. Opioids* - *Requiring any post-operative dosing*		
Any post-operative rescue dosing		x
-Ketorolac vs. Placebo		x
Micrograms of fentanyl required in recovery room	**Favors Ketorolac** WMD=-27.26, 95% CI -49.65 to -3.93	

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APPENDIX B

THE ROLE OF KETOROLAC AND INTRAVENOUS OPIOID IN THE POST-OPERATIVE PEDIATRIC PATIENT: A SYSTEMATIC REVIEW

Background to the Research

Trauma resulting from surgical intervention will always cause some form of post-operative discomfort (Anthony & Jasinski, 2002). Without proper control, this discomfort can escalate to unbearable pain and impede healing and basic functioning of the patient. Managing post-operative pain in the pediatric population presents its own unique set of issues and concerns.

Too often, children experience less than optimal pain management. The causes of sub-optimal pain management are complex and include the child's age, clinical decision making, myths about pain and parental fears. Young children are often unable to vocalize their pain and their need for analgesics (Carney, Nicolette, Ratner, Minerd, & Baesl, 2001) leaving parents and health care professionals to guess the amount of pain medication necessary to keep the child comfortable. Health professionals have a tendency to underestimate or ignore the pain children experience (Schechter, 1999). Inadequate use of analgesics, inability to provide analgesics in a timely manner, and failure to communicate evaluations of pain treatments amongst staff lead to inadequate treatment of pain (Dahl, 2002 Aug; Jacob & Puntillo, 2000 Jul; Rutledge, Donaldson, & Pravikoff, 2002). Ignorance of drug side effects and myths of addiction related to analgesics have resulted in fear of administering analgesics to children. Practitioners' fears of respiratory depression, nausea and vomiting,

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decreased level of consciousness, ileus and urinary retention frequently associated with opioid administration contribute to the routine sub-therapeutic dosing of opioids in pediatrics (Carney et al., 2001). Parents' fears of "over-dosing" children on pain medication, or having children become addicted to opioids also contribute to the inadequate administration of pain medication (Anysley-Green, 1996).

Inadequate treatment of pain in children can have side effects involving the cardiovascular, respiratory, endocrine, metabolic, genitourinary, gastrointestinal, and immune systems (McCaffery & Pasero, 1999). Children may also manifest cognitive and behavioral problems as a direct side effect of uncontrolled pain (Kain et al., 2004 Dec).

With non-steroidal anti-inflammatory drugs (NSAIDs) now available in intravenous form as ketorolac (Toradol™), clinicians who are caring for children's post-operative pain may find a role for non-steroidal anti-inflammatory drugs. These may be the drugs of choice when clinicians are concerned about side effects from opioids, such as respiratory depression, (Watcha et al., 1992, Lieh-Lai et al., 1999, Maunuksela et al., 1992, Carney et al., 2001, Anthony & Jasinski, 2002, Mather & Mckie, 1983, Schechter et al., 1986) nausea and vomiting (Watcha et al., 1992, Lieh-Lai et al., 1999, Carney et al., 2001, Anthony et al., 2002, Keidan et al., 2004, Mendel et al., 1995, Munro et al., 2002, Munro et al., 1994, Romsing, J., 1998, Romsing et al., 1997, Shende, D., 1999), decreased level of consciousness, ileus and urinary retention (Carney et al., 2001, Munro et al., 1994 & Romsing et al., 1997). With the development of

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ketorolac, NSAIDs can now be administered intravenously. Ketorolac provides analgesic effects similar to opioids when used for mild to moderate pain (Watcha et al., 1992, Carney et al., 2001, Mendel et al., 1995, Munro et al., 1994, Munro et al., 2002, Romsing, J., 1998, Shende, D., 1999, Bean-Lijewski & Hunt, 1996, Chauhan et al., 2001, Gunter et al., 1995, Gupta et al., 2005). It also has the added benefits of having anti-pyretic and anti-inflammatory properties (Pendeville, P.E., 1995). On the negative side, clinicians believe that intravenous ketorolac increases risk of post-operative bleeding and many are hesitant to use it (Romsing, J., 1998, Bean-Lijewski & Hunt, 1996, Gunter et al., 1995, Gupta et al., 2005, Judkins et al., 1996, Marret, E., 2004, Rusy et al., 1995, & Splinter et al., 1996). The belief that intravenous NSAIDs increase the risk of post-operative bleeding has arisen from the results of several studies. A single dose of ketorolac increased major post-operative bleeding enough to suggest that it is contraindicated in pediatric adeno-tonsillectomy patients (Gunter et al., 1995). Ketorolac has been reported to increase the number of post-operative bleeding events and the risk of a child experiencing major bleeding episode following tonsillectomy (Gunter et al., 1995). It has also been linked to increased bleeding time (Bean-Lijewski & Hunt, 1996). The results of these studies and a meta-analysis (Marret et al., 2003) of studies of pediatric tonsillectomy led to recommendations that ketorolac not be given to pediatric patients following tonsillectomy.

A systematic review and meta-analysis completed in 2003 by Marret et al led to the recommendation that ketorolac not be used at all in any post-operative

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tonsillectomy patients. However, concerns have been raised by Dsida and Cote (2004) over the quality of the study and the method of data pooling used in the Marret et al meta-analysis. The search for studies for inclusion in the systematic review examined only two databases (MEDLINE and CCTR), excluded all non-English studies, and used a quality of study ranking system which eliminated studies that were thought to be of low quality. The seven studies included in the review had some important variations. The samples included adults and children. Other variations in techniques included: route of administration (oral and parental), number or length of doses (one dose to two weeks of doses), and onset of NSAID treatment (upon completion of surgery or at time of discharge home). These methodological variations can affect the meta-analysis.

Ketorolac is currently available to practitioners caring for patients who have undergone a wide variety of surgical procedures. The many differences between children and adults require that study selection exclude adults when the focus of the review is a pediatric matter. It is appropriate to complete a meta-analysis to examine the risks and benefits ketorolac may have for all post-operative pediatric patients. A more thorough literature search than the previous meta-analysis completed is necessary to ensure that all available relevant research has been included. Subgroup analysis including, high dose ketorolac versus low dose ketorolac, length of treatment and day surgery patients compared to inpatients will provide a more thorough analysis on which practitioners can base prescribing decisions.

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Many excellent reviews have been published about the use of NSAIDs and their effects on postoperative pain in pediatrics (Di Massa, Scardigli, Bruni, & Valentino, 2000 Oct; Forrest, Heitlinger, & Revell, 1997 May; Resman-Targoff, 1990 Nov; J. Romsing & Walther-Larsen, 1997 Jul). With an absence of information about safety and efficacy of intravenous ketorolac in the pediatric population, a systematic review of the literature is appropriate and will potentially shed some light on the question.

Objectives

To examine the role of intravenous ketorolac with regard to safety, side effects, and analgesic benefit in comparison to intravenous opioids or placebo in the post-operative pediatric population.

Criteria for considering studies for this review

Types of participants

This review considered trials involving children less than 18 years of age, of both sexes and all ethnic origins. Children had to be undergoing a surgical procedure that required post-operative intravenous analgesics either as inpatients or day surgery patients. Studies that enrolled children and adults would be included if the data for the children had been separated from that of the adults. Where data for children was not separated from adults, an attempt was made to contact the author to see if the information was available.

Types of interventions

The interventions assessed were post-operative intravenous ketorolac administration, in combination with, or compared to either intravenous opioids or

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an intravenous placebo. Doses had to follow standard pediatric dosage guidelines, and could be either a single or multiple doses.

Types of outcome measures

The primary outcome measures of the review were selected *a priori*:

1. Pain experienced by the children post-operatively as assessed by self-report or observation (using any pain scale).
    A. Self report scales are used for children 3 years of age and older who can rank their pain using validated scales such as:
        a. Faces scale: six cartoon faces showing increasing degrees of distress. Faces 0 signifies "no hurt" and face 5 the "worst hurt you can imagine". The child chooses the face that best describes his or her own pain at the time of assessment. .
        b. Visual analogue scale (VAS) uses a 10 cm line with one end marked as no pain and the opposite end marked as the worst pain. The child makes a mark on the line to illustrate the pain experience. A measure is taken of the distance along the line to the child's mark.
    B. Observational scales are the primary method of pain assessment for infants and children less than 3 yrs old, and for those with developmental disabilities. Validated tools include:
        a. CRIES: Assesses crying, oxygen requirement, increased vital signs, facial expression.

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b. FLACC: (Face, Legs, Activity, Crying, Consolability scale). The scale is used with children from 2 months to 7 years. The score can range from 0-10.

c. CHEOPS: (Children's Hospital of Eastern Ontario Pain Scale) is intended for children 1-7 yrs old. It assesses cry, facial expression, verbalization, torso movement, if child touches affected site, and position of legs. A score ≥ 4 signifies pain.

Secondary outcome measures addressed were:

1. The need for "rescue" dosing and/or adjunctive pain medications.
2. Adverse reactions, focusing specifically on post-operative nausea and vomiting and bleeding. Nausea and vomiting included any recorded post-operative nausea and vomiting event. Bleeding events included any reported post-operative bleeding event, milliliters of blood loss in post-operative drains and the need for re-admission or re-operation due to bleeding.
3. Post-operative maladaptive behavioral changes including behavioral changes, agitation levels, and changes in sleeping patterns (Kain et al., 2004 Dec).
4. Time to discharge from recovery room or from hospital in minutes.

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Types of studies

This review considered only randomized controlled trials. The trials could be of any design (e.g. cross-over or not) and could be published or unpublished. Language restrictions were not imposed.

Search Strategy for identification of studies

A comprehensive search strategy was developed for each database. The search strategy below was developed for MEDLINE and was appropriately adapted for each additional database. Terms were confirmed with a professional librarian who specializes in systematic review search in medicine and the health sciences.

1. opioid.mp. or exp Narcotics
2. Analgesics, Non-Narcotic/ or analgesics.mp. or exp Analgesics/ or Analgesics, Opioid
3. morphine.mp. or exp Morphine/ or Morphine Derivatives
4. (dilaudid or hydromorphone).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
5. (meperidine or pethidine or demerol).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
6. fentanyl.mp. or exp Fentanyl
7. 437-38-7.rn.
8. 57-27-2.rn.
9. (466-99-9 or 71-68-1).rn.

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10. (57-42-1 or 50-13-5 or 28097-96-3).rn.

11. or/1-10

12. Ketorolac Tromethamine/ or exp Ketorolac/ or ketorolac.mp.

13. toradol.mp. or exp Ketorolac Tromethamine

14. (74103-06-3 or 74103-07-4).rn.

15. or/12-14

16. 11 and 15

17. limit 16 to "all child (0 to 18 years)"

Databases searched include: EBM-Reviews-Cochrane central register of controlled trials (up to the 4th quarter of 2005), EBM Reviews - Cochrane Database of Systematic Reviews (up to the 4th quarter of 2005), Cochrane Database of Systematic Reviews: Cochrane Library, (current library as of January 2006), Cochrane Pain, Palliative and Supportive Group Register: (current issue as of January 2006), MEDLINE: (1966-January, 2006), PubMed: (1966 - January, 2006), EMBASE: (1988- January, 2006), CINAHL: (1982-January, 2006), Web of Science: (1975-January 2006), AMED: (1985-January, 2006), EBM Reviews: (1991-January, 2006), International Pharmaceutical Abstracts (1970-January, 2006),. MD Consult: (current database up to January, 2006), National Guideline Clearinghouse (US): (current database up to January, 2006), SAM Online: (current database up to January, 2006), Dissertation Abstracts: 1986-January, 2006), Biosis (current database up to January, 2006), Google Scholar (first 100 hits as of January 26, 2006), Pascal (current database up to January, 2006), SCOPUS(current database up to January, 2006), Clinical

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Evidence(current database up to January, 2006), MEDLINE in Process(current database up to January, 2006), EBMR (current database up to January, 2006), Alberta Heritage Foundation for medical Research (AHFMR): www.ahfmr.ab.ca (current database up to January, 2006), Therapeutics Initiative: www.ti.ubc.ca (current database up to January, 2006), Current Controlled Trials: www.controlled-trials.com (current database up to January, 2006), CenterWatch: www.centerwatch.com (current database up to January, 2006), Clinical Study Results: http://clinicalstudyresults.org (current database up to January, 2006), Clinicaltrials.gov: http://clinicaltrials.gov (current database up to January, 2006), International Register of Clinical Trials Registers: www.trialscentral.org (current database up to January, 2006), Alberta Research Centre for Child Health Evidence (ARCHE): www.ualberta.ca/ARCHE/reviews.html (current database up to January, 2006), and reference lists of articles. The primary authors of the articles who met the basic criteria of the review were also contacted by email or letter to inquire about any published or unpublished articles about which they may have been aware.

Method of the review

Study Selection

Titles, abstracts and medical search headings (MeSH) of all reports identified in the initial search were examined by one reviewer and the full text articles were obtained for the studies that appeared to meet the following inclusion criteria:

a. Patients were children aged 18 years or less

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b. Study evaluated both intravenous ketorolac and either an intravenous opioid or an intravenous placebo.
c. Study was looking at children immediately post-operatively as either an in-patient or day surgery patient

Two reviewers then conducted an in-depth review of the articles to determine whether or not they should be included in the review. Disagreements were resolved by discussion before quality assessment and data extraction occurred.

Quality Assessment

Quality of all included studies was assessed by two independent reviewers at the time of data extraction. All studies were examined using the allocation concealment method and the Jadad scale (Jadad et al., 1996 Feb). This method rates a trial on a scale of A through D. "A" indicates that the randomization technique is adequate (i.e. centralized by telephone or computer system). "B" indicates that the concealment is unclear (i.e. sealed envelopes, but not sequentially numbered or opaque). "C" indicates that the concealment method was inadequate (i.e. open list of random numbers, or day of week), and "D" indicates that allocation concealment was not used.

The Jadad scale (Jadad et al., 1996 Feb) is a five point scale where a point is allocated if, a) the study is described as randomized b) the method of randomization is well described and appropriate c) study outcome assessment is blinded d) the method of blinding is well described and appropriate and e) a description of withdrawals and dropouts from the study is provided. The scale requires the deduction of one point if methods for randomization or blinding are

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inappropriate. Reviewers were not blind to the trial authors, institutions or journal name during the study selection or quality assessment process.

Data Extraction

Data were extracted from included studies by two reviewers who used a data extraction form designed for this review. The reviewers extracted the data independently and then compared the data to ensure no discrepancies.

Eight studies included in this review were either missing data relevant to the study or provided data that could not be combined with data from other studies (Keidan, Zaslansky, Eviatar, Segal, & Sarfaty, 2004; Lieh-Lai, Kauffman, Uy, Danjin, & Simpson, 1999; Maunuksela, Kokki, & Bullingham, 1992; Munro, Riegger, Reynolds, Wilton, & Lewis, 1994; Munro et al., 2002; Park et al., 2000; Pendeville et al., 1995) For example, Pendeville et al. (1995) reported a mean age of 18.6 years (± 3.8 years), but was unable to provide the raw data on those subjects less than 18 years of age.

Additional information was sought from all of the authors via email and/or letter. Five authors responded, but none had access to the data required for the study to be included in the review.

Where means and standard deviations were not available, they were computed using information provided in the article (graph's, figures, or calculated from ranges.)

Data Analysis

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All data were analyzed using a statistical package (RevMan 4.2.8) provided by the Cochrane Collaboration. A random effects model was used to examine heterogeneity among studies with a 95% confidence interval. Heterogeneity was analyzed quantitatively using the I-squared statistic provided by the RevMan software. I-squared statistics examine the variability in the analysis due to between study variability as opposed to within study variability (Brady-Fryer, Wiebe, & Lander, 2004). An I-square greater than 50% is considered large.

When homogeneity among two or more studies was thought to occur, data were pooled using a fixed effects model. Dichotomous data were analyzed and reported as relative risk ratios (RR) with a 95% confidence interval and a fixed effects model. Where small event rates occurred, Peto odds ratio was used with a fixed effects model.

Continuous data were analyzed and reported as weighted means differences (WMD) where the units examined were combinable. When the units were incompatible, the standardized mean difference (SMD) was computed.

Description of the studies

The initial search identified 1637 publications. A review of abstracts led to exclusion of 1564 of these publications for at least one of the following reasons: adult subjects (n=647), non-randomized controlled trial (n=503), non-human subjects (n=34), ketorolac used as an adjunctive medication (n=380). Eighty-eight full text articles were obtained and reviewed by two independent reviewers. An additional 73 studies were excluded from the review for the following reasons:

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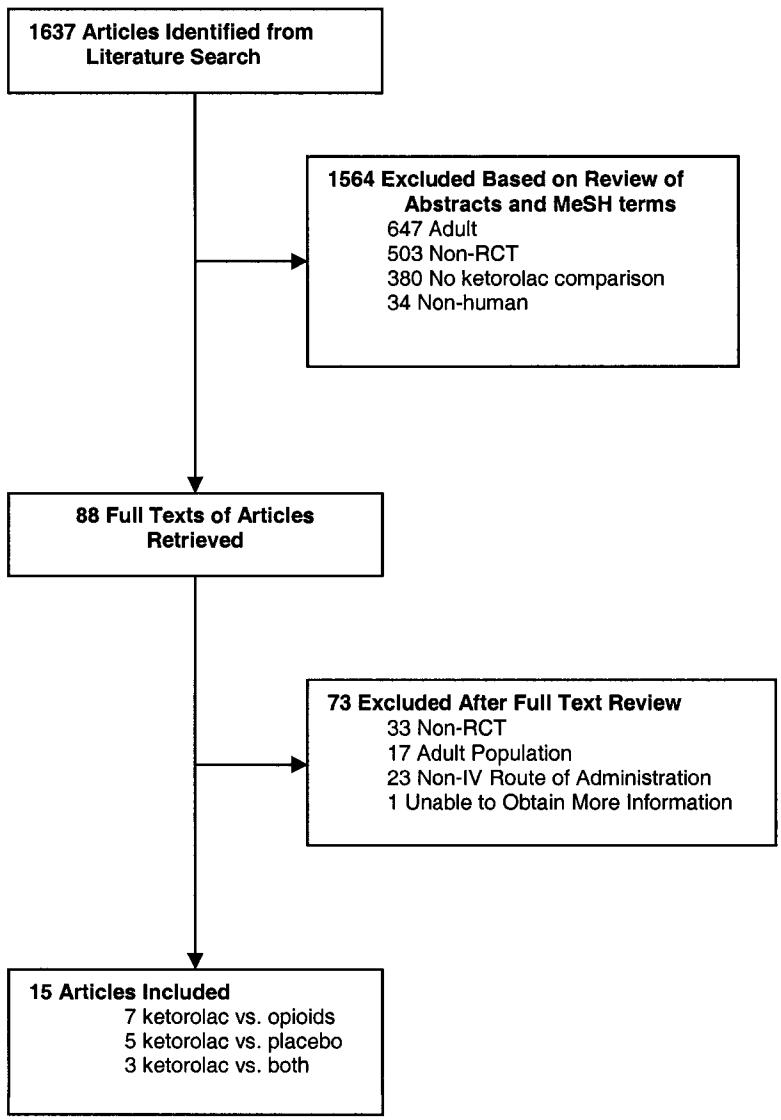
non-randomized controlled trials (n=33), adult patients (n=17) and non-intravenous route of drug administration (n=23). One other study was excluded because the pediatric data could not be separated from the adult data [20]. Reference lists of the full text articles were examined to make certain that the search was complete. The authors were contacted and asked if they were aware about any published or unpublished articles on the topic of the systematic review. Figure A-1 illustrates the selection and exclusion of studies for this systematic review.

Figure A-1. Summary of article selection process.



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Fifteen studies were included in this systematic review yielding 1022 post-operative pediatric patients requiring intravenous pain mediations (Chiaretti et al., 1997; Gunter et al., 1995; Gupta et al., 2005; Keidan et al., 2004; Lieh-Lai et al., 1999; Maunuksela et al., 1992; Mendel et al., 1995; Munro et al., 1994; Munro et al., 2002; Park et al., 2000; Purday, Reichert, & Merrick, 1996; J. Romsing, 1998; Shende, 1999; Sutters, Shaw, Gerardi, & Hebert, 1999; Watcha, Jones, Lagueruela, Schweiger, & White, 1992). None of the studies included patients less than 1 year of age. Where reported, patients' ASA status was 1 or 2. Details of each study are given in the Table A-2 - characteristics of included studies.

Seven of the studies compared intravenous ketorolac with opioids (Chiaretti et al., 1997; Gunter et al., 1995; Keidan et al., 2004; Lieh-Lai et al., 1999; Munro et al., 1994; Purday et al., 1996; Shende, 1999), five compared with placebo (Gupta et al., 2005; Munro et al., 2002; Park et al., 2000; J. Romsing, 1998; Sutters et al., 1999), and three compared with both (Maunuksela et al., 1992; Mendel et al., 1995; Watcha et al., 1992). For the trials including a placebo, identical volumes of normal saline were used for comparison and in all cases the subjects received another form of pain medication.

Fourteen of the studies provided information on post-operative pain although in various ways (Chiaretti et al., 1997; Keidan et al., 2004; Lieh-Lai et al., 1999; Maunuksela et al., 1992; Mendel et al., 1995; Munro et al., 1994; Munro et al., 2002; Park et al., 2000; Purday et al., 1996; J. Romsing, 1998; Shende, 1999). Some of the studies measured pain in more than one way.

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Fourteen studies provided information on the need for "rescue dosing" or adjunctive medications post operatively (Gunter et al., 1995; Gupta et al., 2005; Keidan et al., 2004; Lieh-Lai et al., 1999; Maunuksela et al., 1992; Mendel et al., 1995; Munro et al., 1994; Munro et al., 2002; Park et al., 2000; Purday et al., 1996; J. Romsing, 1998; Shende, 1999; Sutters et al., 1999; Watcha et al., 1992).

Eleven studies reported post-operative bleeding events (Gunter et al., 1995; Gupta et al., 2005; Keidan et al., 2004; Lieh-Lai et al., 1999; Mendel et al., 1995; Park et al., 2000; Purday et al., 1996; Shende, 1999; Sutters et al., 1999; Watcha et al., 1992). Two studies reported milliliters of blood loss (Munro et al., 2002; J. Romsing, 1998).

Seven studies reported time to discharge from hospital (Gunter et al., 1995; Gupta et al., 2005; Mendel et al., 1995; Munro et al., 1994; Munro et al., 2002; Purday et al., 1996; Sutters et al., 1999) and four reported time to discharge from the recovery room (Gunter et al., 1995; Munro et al., 2002; Purday et al., 1996; Watcha et al., 1992).

Thirteen studies reported post-operative nausea and vomiting events (Gunter et al., 1995; Keidan et al., 2004; Lieh-Lai et al., 1999; Maunuksela et al., 1992; Mendel et al., 1995; Munro et al., 1994; Munro et al., 2002; Park et al., 2000; Purday et al., 1996; J. Romsing, 1998; Shende, 1999; Sutters et al., 1999; Watcha et al., 1992). One study reported on post-operative maladaptive behaviors (Keidan et al., 2004).

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Methodological quality

All of the studies included in the review were described as randomized controlled trials. Thirteen of the studies had an allocation concealment that was unclear, making it difficult to ensure that the randomization was completely blinded (Chiaretti et al., 1997; Gunter et al., 1995; Gupta et al., 2005; Keidan et al., 2004; Lieh-Lai et al., 1999; Maunuksela et al., 1992; Mendel et al., 1995; Munro et al., 1994; Munro et al., 2002; Park et al., 2000; Purday et al., 1996; J. Romsing, 1998; Shende, 1999). Only two of the included studies had an allocation concealment method that was deemed adequate (Gunter et al., 1995; Sutters et al., 1999) (see table A-2– Characteristics of Included Studies).

Nine studies were considered to be of high quality when evaluated using a Jadad score ≥3 (Gunter et al., 1995; Keidan et al., 2004; Lieh-Lai et al., 1999; Maunuksela et al., 1992; Munro et al., 2002; Park et al., 2000; J. Romsing, 1998; Sutters et al., 1999; Watcha et al., 1992). Only one study received a Jadad score of 4 (Gunter et al., 1995). Of the six low quality studies, four studies received a score of 2, (Chiaretti et al., 1997; Gupta et al., 2005; Munro et al., 1994; Purday et al., 1996) and two studies received a score of 1 (Mendel et al., 1995; Shende, 1999).

Results

Ketorolac versus opioid comparisons

Results are presented in six main categories 1) pain 2) "rescue dosing" or PRN medications 3) time to discharge 4) post-operative nausea and vomiting 5) bleeding events and 6) post-operative maladaptive behaviors. Subgroup

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analyses for each category are presented in Figure 1-2, which is a flow diagram summarizing ketorolac versus opioid comparisons. The results reported on the following pages are summarized in Table A-1.

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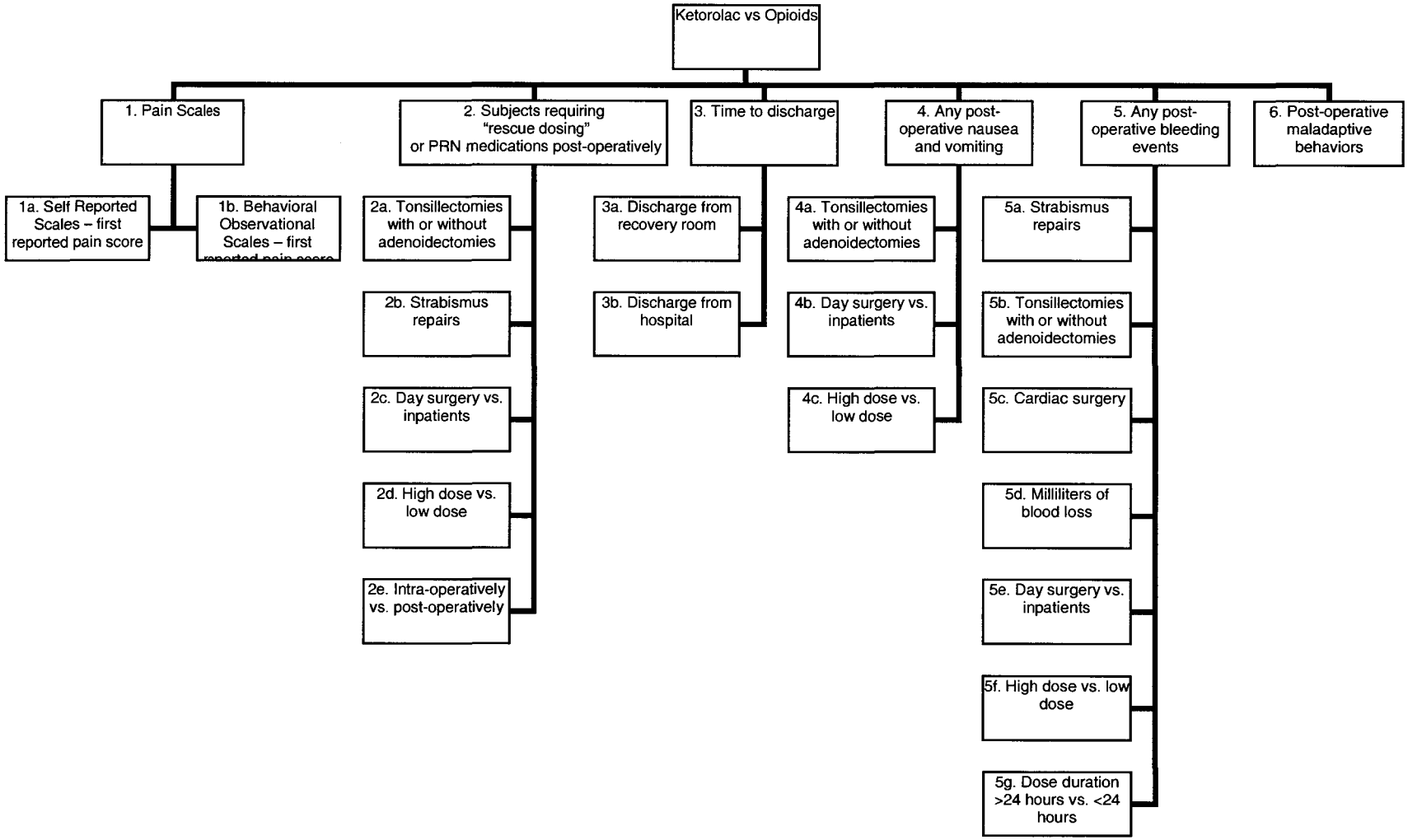
Figure A-2. Flow diagram of ketorolac versus opioid comparisons.



1. Pain Scores

a. Observational pain scales

The Objective Pain Scale is an observational pain scale. Although this scale has not been psychometrically developed, it was widely used by researchers who investigated the use of ketorolac. Scores can range from 0-10, zero being no or minimal pain and ten being severe pain. A score of 0-2 is applied to the following five categories, 1) blood pressure (increased by 10%, 10-20%, 20-30%, 2) crying (not crying, crying but consolable, inconsolable), 3) moving (none, restless, thrashing), 4) agitation (calm, mild, hysterical), and 5) verbal response or body language (asleep or states had no pain, unable to localize or states had mild pain, localizes or state has moderate to severe pain). Four trials (Mendel et al., 1995; Purday et al., 1996; Shende, 1999; Watcha et al., 1992) examined pain scores using the objective pain scale. No statistically significant differences were found for pain for ketorolac versus opioids (see Figures A-4).

One study (Lieh-Lai et al., 1999) used a unique observational pain scale when comparing Ketorolac with opioids. *P*ain scores did not differ when comparing ketorolac and opioids (see Figure A-5).

2. Rescue Dosing

Seven studies (Gunter et al., 1995; Lieh-Lai et al., 1999; Maunuksela et al., 1992; Mendel et al., 1995; Munro et al., 1994; Purday et al., 1996; Shende, 1999) examined the need for adjunctive pain medication or "rescue dosing" in the

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post operative period and found no statistical significance when ketorolac was compared with opioids (see Figure A-6).

No statistical difference was found when comparing ketorolac versus opioids in tonsillectomy patients (see Figure A-6). (Gunter et al., 1995; Keidan et al., 2004) ,strabismus repair patients (see Figure A-6). (Mendel et al., 1995; Munro et al., 1994; Shende, 1999) inpatients versus (Lieh-Lai et al., 1999; Maunuksela et al., 1992) day surgery patients (see Figure A-7)(Gunter et al., 1995; Keidan et al., 2004; Mendel et al., 1995; Munro et al., 1994; Purday et al., 1996; Shende, 1999) or the use of high dose Ketorolac (>=0.6 mg/kg/dose) (Gunter et al., 1995; Keidan et al., 2004; Lieh-Lai et al., 1999; Mendel et al., 1995; Munro et al., 1994; Purday et al., 1996; Shende, 1999) versus low dose Ketorolac (<=0.5 mg/kg/dose) (see Figure A-8) (Maunuksela et al., 1992) . No statistical difference was found for ketorolac and opioids in studies that examined intra- or pre-operative administration of ketorolac (Keidan et al., 2004; Mendel et al., 1995; Munro et al., 1994; Purday et al., 1996; Shende, 1999) with post-operative administration (see Figure A-9) (Gunter et al., 1995; Lieh-Lai et al., 1999; Maunuksela et al., 1992).

3. Time to discharge

Three studies (Gunter et al., 1995; Purday et al., 1996; Watcha et al., 1992) provided information on discharge time from the recovery room or PARR. No statistical difference was found in discharge time for the opioid and ketorolac groups (see Figure A-10).

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Five studies (Gunter et al., 1995; Gupta et al., 2005; Mendel et al., 1995; Munro et al., 1994; Purday et al., 1996) provided data about time to discharge from hospital. This was not statistically different for ketorolac when compared with opioids (see Figure A-11), nor was it significant when ketorolac and opioids were compared for time to discharge for inpatients or day surgery patients (see Figure A-12).

4. Nausea and Vomiting

Data about nausea and vomiting were included in nine studies (Gunter et al., 1995; Keidan et al., 2004; Lieh-Lai et al., 1999; Mendel et al., 1995; Munro et al., 1994; Purday et al., 1996; Shende, 1999; Watcha et al., 1992). Those who received ketorolac versus opioids had significantly less nausea and vomiting (RR=0.63; 95% CI 0.51 to 0.77). The number needed to treat (NNT) was 6 (see Figure A-13).

Subgroup analysis of three studies examining patients undergoing strabismus repair surgery show a statistically significant favoring of Ketorolac over opioids in reducing nausea and vomiting post-operatively (RR=0.28; 95% CI 0.15 to 0.53, NNT=3) (see Figure A-13). However the occurrence of nausea and vomiting for ketorolac and opioids did not differ in studies of tonsillectomies (Gunter et al., 1995; Keidan et al., 2004) (see Figure A-13).

Studies providing data on day surgery patients (Gunter et al., 1995; Keidan et al., 2004; Mendel et al., 1995; Munro et al., 2002; Purday et al., 1996; Shende, 1999) showed a statistically significant reduction in the amount of post-operative nausea and vomiting for ketorolac (RR 0.48; 95% CI 0.38 to 0.61,

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NNT=4), whereas the three studies examining inpatients (Lieh-Lai et al., 1999; Maunuksela et al., 1992; Watcha et al., 1992) did not (see Figure A-14).

High doses of ketorolac (≥ 0.6 mg/kg) were examined in eight studies (Gunter et al., 1995; Keidan et al., 2004; Lieh-Lai et al., 1999; Mendel et al., 1995; Munro et al., 1994; Purday et al., 1996; Shende, 1999; Watcha et al., 1992). Significantly less nausea and vomiting in the ketorolac group versus the opioid comparison was found (RR=0.63, 95%CI 0.51 to 0.78). Maunuksela et al. (1992) examined low dose ketorolac (≤ 0.5 mg/kg) and did not find a statistical difference between ketorolac and opioids (see Figure A-15).

5. Bleeding events

No statistical difference in bleeding for ketorolac and opioids was found among the eight studies(see Figure A-16) (Gunter et al., 1995; Keidan et al., 2004; Lieh-Lai et al., 1999; Mendel et al., 1995; Purday et al., 1996; Shende, 1999; Watcha et al., 1992). No difference in bleeding occurred for tonsillectomy (see Figure A-16) (Gunter et al., 1995; Keidan et al., 2004), or strabismus repair (see Figure A-16) (Mendel et al., 1995; Shende, 1999).

Gupta et al., (2005) examined milliliters of blood loss in drains post-operatively. The analysis identified a statistically significant difference (WMD -3.20 (95% CI -5.49 to -0.91) favoring the use of ketorolac (see Figure A-17). While it is true that this meta-analyses indicated significantly greater loss of blood (as measured in a drain), the results cannot be considered to be conclusive. Only a single study with a small sample size (n=35 per group) was available for

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analysis. Mean bleeding time did not provide a statistical difference between ketorolac and opioids (see Figure A-18) (Lieh-Lai et al., 1999).

No statistical difference was found in bleeding for ketorolac and opioids for the following: re-operation or readmission to hospital (see Figure A-19), inpatients versus outpatients (see Figure A-20), or high dose versus low dose ketorolac (see Figure A-21).

The half life of ketorolac is approximately 2 hours, with five to six drug half lives needed to deplete the anti-platelet effect (Dsida & Cote, 2004). This led to the question, will patients who have been on the drug for only a short amount of time have less bleeding events in the overall course of their treatment than those who have been administered the drug for a prolonged period of time (duration greater than 24 hours versus less than 24 hours). The half life of ketorolac is approximately 2 hours, with it taking five to six drug half lives to deplete the anti-platelet effect (Dsida & Cote, 2004). This led to the question, will patients who have been on the drug for only a short amount of time have less bleeding events in the overall course of their treatment than those who have been administered the drug for a prolonged period of time. No difference was found when examining bleeding events and dose duration greater than 24 hours versus less than 24 hours (see Figure A-22).

6. Post-Operative Maladaptive Behaviors

There was no statistical difference in post-operative behavioral changes when comparing ketorolac and opioids (Keidan et al., 1995). Significantly less agitation in recovery room (RR, 1.92; 95% CI, 1.15 to 3.20) (see Figure A-23)

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and less sleep disturbances the night of surgery was found in the opioid comparison group (RR, 1.76; 95% CI, 1.07 to 2.89) (see Figure A-24).

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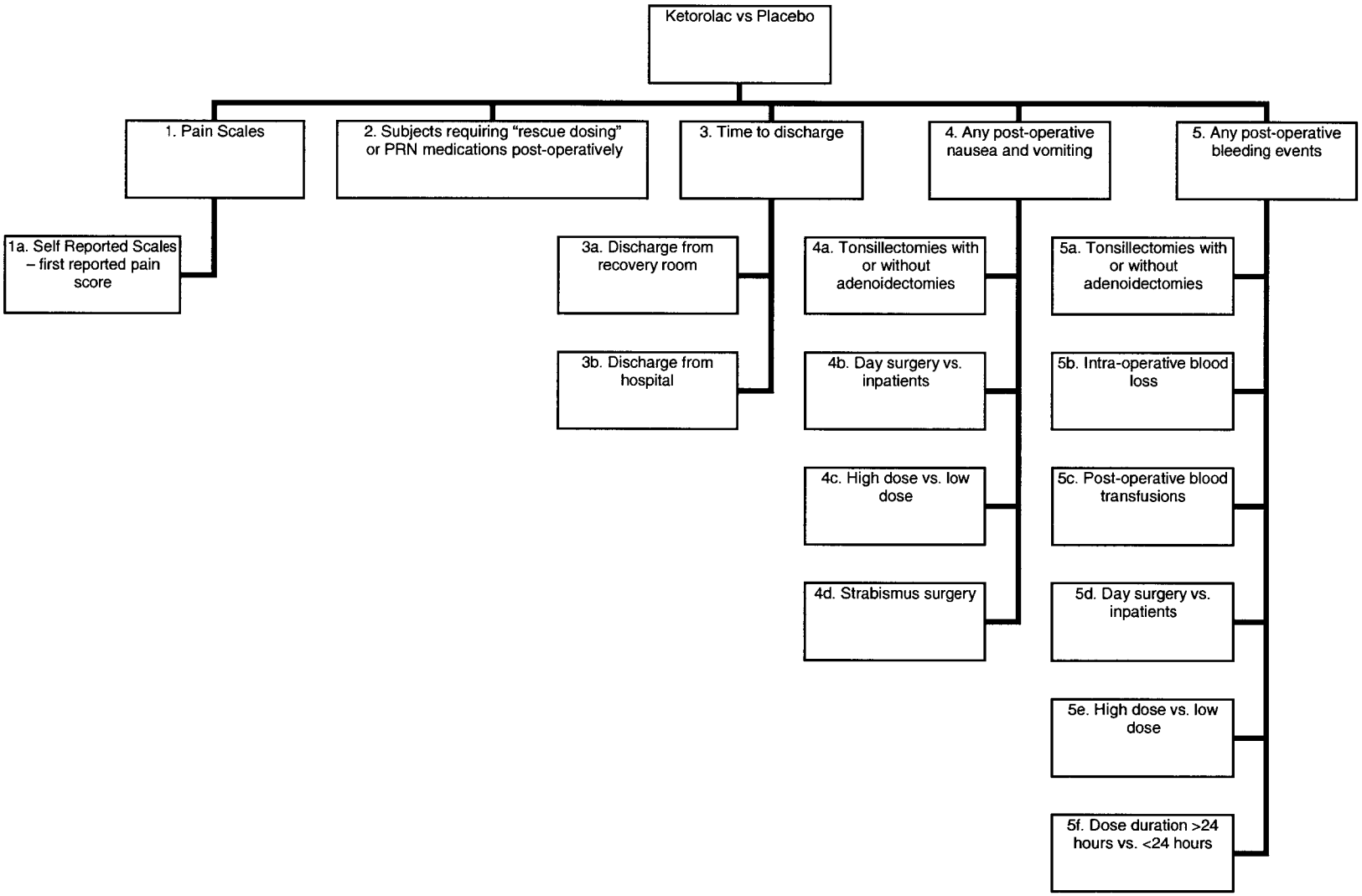
Figure A-3. Flow diagram of ketorolac versus placebo comparisons.



Ketorolac versus placebo comparisons

Results are presented in five main categories 1) pain scales 2) "rescue dosing" or PRN medications 3) time to discharge 4) post-operative nausea and vomiting and 5) bleeding events. Subgroup analysis for each category is presented in the flow diagram of ketorolac versus placebo comparisons (Figure A-3).

1. Pain Scales

1a. Self-Reported Pain Scales

The poker chip pain scale was used to compare ketorolac versus placebo (J. Romsing, 1998 (WMD -0.75; 95% CI -1.22 to -0.28) (see Figure A-25). Pain was significantly less in the ketorolac group versus the placebo group. When looking at self-reported post-operative bladder spasms, Park et al (2000) found that the occurrence was significantly less in the ketorolac group than the placebo comparison (RR 0.3' 95% CI, 0.11 to 0.83) (see Figure A-27).

2. Rescue Dosing

No difference was found for ketorolac versus placebo in the need for rescue dosing post-operatively (Mendel et al., 1995) (see Figure A-28). Sutters et al. (1999) examined micrograms per kilogram of fentanyl required post-operatively and found the ketorolac group favoured over the placebo group [WMD -27.26; 95% CI -49.65 to -3.93] (see Figure A-29). Thus, fentanyl requirements were lower in the ketorolac group compared to placebo group.

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3. Time to Discharge

Patients receiving ketorolac compared with placebo were discharged earlier from the recovery room (Munro et al., 2002; Watcha et al., 1992) (WMD -10.62; 95% CI -71.97 to -11.79) (see Figure A-30), but not from hospital (see Figure A-31).

4. Nausea and Vomiting

Five studies (Mendel et al., 1995; Park et al., 2000; J. Romsing, 1998; Sutters et al., 1999; Watcha et al., 1992) compared ketorolac patients with placebo patients for any post-operative nausea and vomiting event, and found no statistical difference among the groups (see Figure A-32). Subgroup analysis of tonsillectomy patients (see Figure A-32), and strabismus repair patients (see Figure A-32) found no difference between ketorolac and placebo. Day surgery versus inpatients (see Figure A-33) and high dose ketorolac versus low dose ketorolac patients (see Figure A-34) also showed no difference when comparing ketorolac and placebo.

5. Bleeding Events

Five studies (Mendel et al., 1995; Park et al., 2000; J. Romsing, 1998; Sutters et al., 1999; Watcha et al., 1992) examined any bleeding event post operatively. No significant difference was found (see Figure A-35).

There was no statistical difference between placebo and ketorolac when examining intra-operative blood loss (see FigureA-36), post-operative transfusions(see Figure A-37), readmission to hospital (see Figure A-38), day

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surgery versus inpatients (see Figure A-39), high dose versus lose dose ketorolac (see Figure A-40), and dose duration (>24 hours versus <24 hours) (see Figure A-41).

Discussion

This meta-analysis has produced three main findings that will be of interest to practitioners who work with post surgical pediatric patients. The first significant result is that ketorolac provides no greater risk of post-operative bleeding to patients than opioids or placebo comparisons. The second is that there is a significant reduction of nausea and vomiting in patients receiving ketorolac instead of opioids. And third is that pain control is found to be equivalent when comparing ketorolac and opioids in mild to moderate pain.

Concerns about the potential for ketorolac to cause post-operative bleeding have caused practitioners to be reluctant to prescribe it in a pediatric setting. These concerns are significant enough for the license for intra-operative use of ketorolac to be removed in the United Kingdom. This meta-analysis does not find an increased risk of post-operative bleeding when ketorolac is used. Problems with analysis in the past may have been that when analyzing studies statistically, small sample sizes and small event rates were not considered. Also, differences in surgeries, doses, and frequency and route of administration were grouped together in one analysis group inappropriately.

Ketorolac when compared with opioids is found to have a statistically significant lower incidence of and less severe post-operative vomiting. Nausea

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and vomiting is an established side effect of opioids. Use of ketorolac can be beneficial for surgical procedures where post-operative retching and vomiting can be hazardous, such as with tonsillectomies, strabismus repairs and neurosurgeries.

The findings of several studies have caused a controversy about the potential for post-operative use of ketorolac to cause bleeding [18,25]. In fact, Gunter et al.[18] elected to stop their trial early due to concerns about bleeding caused by ketorolac. This is an example of a single study, with a low frequency event, having a larger impact on clinical behavior than may be warranted. Seemingly significant findings can be caused by a number of confounds (from design problems, to inadvertent biases, to statistical methods). One possibility here is surgical skill level as some of the procedures in the Gunter et al study were carried out by surgical residents. The approach for categorizing "major bleeding" may also have created problems. The major bleeding category only involved one patient requiring re-operation in the first 24 hours. The other 4 patients required further evaluation by medical staff, with one patient being discharged from the emergency room and three admitted to hospital. It would be interesting to learn if the patients who required readmission to the hospital for major bleeding had a significant drop in post-operative hemoglobin to correlate with the diagnosis. The re-operation for the subject in the ketorolac group came on post-operative day 5 which would be difficult to attribute to the drug itself as the anti-platelet effect does not last longer than 24 hours.

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Ketorolac is equivalent to opioids for pain control in mild to moderate pain, without the associated side effects of respiratory depression, bradycardia, urinary retention, or constipation found with opioid use.

Conclusions

Implications for practice

Ketorolac has been thought to be associated with post-operative bleeding and its use avoided in pediatrics. It has been removed from use in the intra-operative formulary in the United Kingdom because of the risk of bleeding. This review and meta-analysis indicate that fears about bleeding with use of ketorolac are without foundation. Ketorolac provides as good pain control as opioids do and no greater risk of bleeding. It also causes less nausea and vomiting than opioids. Ketorolac should be considered for use particularly for surgical procedures where post-operative vomiting is a concern. Patients receiving ketorolac were found to have less pain, require less rescue dosing, and a quicker discharge from recovery room, with no increase in negative side effects, than those receiving placebo. This fact should encourage practitioners to also consider prescribing ketorolac as an adjuvant to intravenous opioids for the opioids sparring effect, where they would have previously not. It should also be used in day surgery so that parents can travel home without fear that the child will vomit during the trip.

This is a good example of clinical decisions being made on the basis of individual studies. Sometimes research with small sample sizes and infrequent

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events (often happening in pediatric studies) will produce results that do not stand up. A meta-analysis may help practitioners to make informed decisions for their patients in an efficient and effective manner while avoiding small event size bias.

Implications for research

Many different methods of observing and recording pain scores are used and not all of them are recognized scales. It would be beneficial for future research if pain scales were standardized so that systematic review and meta-analysis could be carried out more efficiently.

There is much debate as to whether ketorolac causes a delay in bone healing in orthopedic patients. The current research examining this concern is on animal models, or adult patients. In the future, randomized control trials of pediatric patients need to be completed in order to resolve the issue.

In this systematic review only intravenous ketorolac was examined. A systematic review about the safety, side effects and benefits of oral ketorolac when used in day surgery patients would be valuable.

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Table A-1. Summary of Meta-Analysis Findings Comparing Ketorolac versus Opioids

	Statistically Significant	Not Statistically Significant
Pain Scores – *First reported pain score*		
Self reported Pain Scales		*
Observational pain scales		*
Rescue Dosing – *Requiring any post-operative dosing*		
Any post-operative rescue dosing		*
Tonsillectomy patients		*
Day Surgery vs. Inpatients		
High dose ketorolac vs. Low dose ketorolac		*
Intra/Pre-operative dosing vs. Post-operative dosing		*
Time to Discharge – *In minutes*		
Discharge from recovery room or PARR		*
Discharge from hospital		*
Inpatients versus day surgery patients		*
Nausea and Vomiting – *Any reported post-operative nausea and vomiting*		
Any post-operative nausea and vomiting	**Favors Ketorolac** RR=0.63, 95% CI 0.51 to 0.77	
Strabismus repair patients	Favors Ketorolac RR=0.28, 95% CI 0.15 to 0.53	
Tonsillectomy patients		*
Day surgery patients	**Favors Ketorolac** RR=0.48, 95% CI 0.38 to 0.61	
Inpatients		*
High dose ketorolac	**Favors Ketorolac** RR=0.63, 95& CI 0.51 to 0.78	
Low dose ketorolac		*
Bleeding Events – *Any reported post-operative bleeding event*		
Any post-operative bleeding event		*
Tonsillectomy patients		*
Strabismus repair patients		*
Milliliters of blood loss in post-operative drains	**Favors Ketorolac** WMD=-3.20, 95% CI 5.49 to-0.91	
Post-operative bleeding times		*

Table A-1. Summary of Meta-Analysis Findings Comparing Ketorolac versus Opioids Cont.

Patients requiring re-admission/re-operation due to bleeding		*
Inpatients versus outpatients		*
High dose versus low dose ketorolac		*
Dose duration <24 hours versus >24 hours		*
Post-operative maladaptive behaviors		
Agitation level in recovery room	**Favors Opioids** RR=1.92, 95% CI 1.15 to 3.20	
Sleep disturbances the night of surgery	**Favors Opioids** RR=1.76, 95% CI 1.07 to 2.89	

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Table A-2. Summary of Meta-Analysis Findings Comparing Ketorolac versus Placebo

	Statistically Significant	Not Statistically Significant
Pain Scores – *First reported pain score*		
Poker Chip Scale	**Favors Ketorolac** WMD=-0.75, 95% CI -1.22 to -0.28	
Objective pain scales	**Favors Ketorolac** WMD=-1.21, 95% CI -1.21 to -0.51	
Self reported bladder spasms	**Favors Ketorolac** RR=0.30, 95% CI 0.11 to 0.83	
Rescue Dosing – *Requiring any post-operative dosing*		
Any post-operative rescue dosing		*
Micrograms of fentanyl required in recovery room	**Favors Ketorolac** WMD=-27.26, 95% CI -49.65 to -3.93	
Time to Discharge – *In minutes*		
Discharge from recovery room or PARR	**Favors Ketorolac** WMD=10.62, 95% CI -71.97 to -11.79	*
Discharge from hospital		*
Nausea and Vomiting – *Any reported post-operative nausea and vomiting*		
Any post-operative nausea and vomiting		*
Strabismus repair patients		*
Tonsillectomy patients		*
Day surgery patients versus Inpatients		*
High dose ketorolac vs low dose ketorolac		*
Bleeding Events – *Any reported post-operative bleeding event*		
Any post-operative bleeding event		*
Intra operative blood loss		*
Patients requiring ost-operative blood transfusion		*
Patients requiring re-admission/re-operation due to bleeding		*
Inpatients versus day surgery patients		*
High dose versus low dose ketorolac		*
Dose duration <24 hours versus >24 hours		*

Table A-3. Characteristics of Excluded Studies

Study	Reason for exclusion
(Anthony & Jasinski, 2002)	Non-RCT
(Bailey, Sinha, & Burgess, 1997)	Adult IM injection
(Bean & Hunt, 1992)	IM injection
(Bean-Lijewski & Hunt, 1996)	IM injection
(Bravo, Mattie, Spierdijk, Bovill, & Burm, 1988)	IM injection
(Brown, Moodie, Wild, & Bynum, 1990)	Adult
(Burd & Tobias, 2002)	Non RCT
(Camu, Van Overberge, Bullingham, & Lloyd, 1990)	Adult patients
(Cardwell, Siviter, & Smith, 2005)	Systematic review
(Carney, Nicolette, Ratner, Minerd, & Baesl, 2001)	Non-RCT
(Cepeda, Vargas, Ortegon, Sanchez, & Carr, 1995 Jun)	Adult
(Chauhan, Charles, & Noe, 2001)	Non RCT
(Chhabra, 2005)	IM administration
(Centre for Reviews and Dissemination, 2006)	Systematic review
(Dawson, Egbert, & Myall, 1996)	Unable to contact
(J. R. DeAndrade, Maslanka, Maneatis, Bynum, & Burchmore, 1994 Feb)	Review
(J. R. DeAndrade et al., 1996)	IM administration
(Dsida, 2004)	Editorial
(Eberhard & Mora, 2004)	Non-RCT
(Eberson, Pacicca, & Ehrlich, 1999)	Non-RCT
(Fitz-James et al., 1995)	IM route
(Forrest, Heitlinger, & Revell, 1997 May)	Review
(Fricke, Angelocci, Fox, MacHugh, & Yee, 1992)	IM injection
(Geisslinger et al., 1996 Oct)	Adult
(Gillies, Kenny, Bullingham, & McArdle, 1987 Jul)	Adult
(Glassman et al., 1998 Apr 1)	Adult IM
(Gora-Harper, Record, Darkow, & Tibbs, 2001)	Non RCT Adult
(Graham & Wandless, 1995)	No IV opioid (Wound infiltration with 0.5% bupivicaine)
(Greco, 2005)	Non RCT
(Gupta, Daggett, Drant, Rivero, & Lewis, 2004)	Non RCT
(Hackmann, 2004)	Comment/Letter
(Houck, Wilder, McDermott, Sethna, & Berde, 1996 Aug)	Chart review

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Table A-3. Characteristics of Excluded Studies Cont.

(Jelinek, 2000)	Editorial
(Kenny, McArdle, & Aitken, 1990)	Adult
(Kinsella et al., 1992)	IM administration
(Kokki & Salonen, 2002)	No toradol comparison
(Kwon, Kim, Shin, & Kim, 1999)	Unable to contact for more information
(Mack, Hass, Lavyne, Snow, & Lien, 2001)	Adult
(Marret, Antoine, Samama, & Bonnet, 2003)	Systematic review
(Mason, 1993)	Non RCT
(Mather & Peutrell, 1995)	No ketorolac comparison
(McCann & Stanitski, 2004)	Non RCT
(Moiniche, Romsing, Dahl, & Tramer, 2003)	Systematic review
Moyao-Garc, 2004	Non-RCT
(Munro, Malviya, Lauder, Voepel-Lewis, & Tait, 1999)	Chart review
(O'Hara, Fragen, Kinzer, & Pemberton, 1987 May)	Adult IM injection
(Olkkola & Maunuksela, 1991 Feb)	No comparison to placebo or opioid
(Pappas, Fluder, Creech, Hotaling, & Park, 2003)	No IV ketorolac
(Pendeville et al., 1995)	Request for information returned. Unable to obtain data on pediatric patients
(Perttunen, Nilsson, & Kalso, 1999)	Adult
(Picard, Bazin, Conio, Ruiz, & Schoeffler, 1997 Dec)	Adult
(Ready et al., 1994 Jun)	Adult Review
(Reinhart et al., 1993 May-Jun)	IM adult
(Reuben, Connelly, & Steinberg, 1997 Jul-Aug)	Adult
(Reuben, Connelly, Lurie, Klatt, & Gibson, 1998 Jul)	Adult
(Richter, Valley, Bailey, Feid, & Calhoun, 1992)	IM injection
(Romsing & Walther-Larsen, 1997 Jul)	Review
(Schechter, 1999)	Non-RCT
(Soler Company, Faus Soler, Montaner Abasolo, & Morales Olivas, 2001)	Non-RCT
(Splinter, Reid, Roberts, & Bass, 1997)	
(Stanski, Cherry, Bradley, Sarnquist, & Yee, 1990)	IM administration route
(Stouten et al., 1992 Oct)	Adult
(Strom et al., 1996 Feb 7)	Non-RCT
(Sutters, Levine, Dibble, Savedra, & Miaskowski, 1995)	IM administration
(Thwaites et al., 1995 Jul)	Adults
(Varrassi et al., 1994 Mar)	Adult/Review

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Table A-3. Characteristics of Excluded Studies Cont

(Vetter & Heiner, 1994)	No comparison
(Vintar, Rawal, & Veselko, 2005)	Adults
(Watcha, Jones, Lagueruela, Schweiger, & White, 1992)	Editorial
(Weinstein, Nicolson, & Schreiner, 1994)	No comparison for ketorolac

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Table A-4. Characteristics of Included Studies

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Chiaretti,1997	• Prospective randomized controlled trial	• 52 patients • Age: 66.6 ± 70.5 mo* • Inpatients	• A) Ketorolac 1.2 mg/kg q6h • B) Ketorolac 1.2 mg/kg (bolus) + 0.21 mg/kg/hr • C) Fentanyl 1 mcg/kg/hr • D) Fentanyl 1 mcg/kg/hr + Ketorolac 0.21 mg/kg/hr	• Best pain control in Ketorolac and Fentanyl group	Jadad score: 2	B
Gunter, 1995	• Double blind, • Prospective, randomized controlled trial	• 97 patients • Age: 71.5 ± 30.5 mo • Tonsillectomy • Day surgery	• Ketorolac 1mg/kg • Morphine 0.1 mg/kg	• No decrease in awakening time, time to readiness for discharge, or readmission between both groups. • Patients receiving morphine were more likely to experience emesis after leaving the RR than the ketorolac group	Jadad score: 4 • Study stopped after first 96patients due to bleeding concerns.	A

* Unless otherwise noted, age is presented in pooled mean ± standard deviation

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Table A-4. Characteristics of Included Studies Cont.

Gupta et al, 2005	• Prospective, randomized controlled trial	• 72 patients • Age: 24.1 ± 33.8 mo • Surgery for congenital heart disease	• Ketorolac 0.5 mg/kg Q6h ATC • No ketorolac	• Short term use of ketorolac (<48 hrs) is not associate with and increase in bleeding complications	Jadad score:2	B
Keidan et al, 2004	• Double blind • Prospective, randomized controlled trial	• 57 patients • Age: 4.95 ± 2.6 yr • Surgery: adenoidectomy and laser-assisted tonsillectomy	• Ketorolac 1 mg/kg • Fentanyl 2 μg/kg	• There was no statistical difference between Fentanyl and Ketorolac in N&V, or pain scores. • The ketorolac group had higher agitation scores in recovery.	Jadad score: 3	B
Lieh-Lai, 1999	• Prospective, • Randomized, • Double-blind • Parallel • Single-dose • Positive control study	• 102 patients • Age: 10.4 ± 4.4 years • Admitted to the intensive care unit post-operatively	• Ketorolac 0.6 mg/kg • Morphine 0.1 mg/kg	• No difference between group concerning pain control, rescue dose requirements, bleeding time or vital signs. • More patients in the ketorolac experienced N&V than the morphine group. • More patients in the morphine group never achieved pain relief than in the ketorolac group.	Jadad score: 3	B

[$] Age presented in median (range)

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Table A-4. Characteristics of Included Studies Cont.

Maunuksela, 1992	• Double blind • Randomized parallel-group study	• 92 patients, • Age: 7 (3-12) yr[$] • Elective surgery and understand the pain scoring scale	• Morphine 0.1mg/kg • Ketorolac 0.2 mg/kg + 0.2 mg/kg, + 0.1 mg/kg • Ketorolac 0.5 mg/kg followed by 2 doses of placebo	• No statistically significant difference in pain scores • Less doses of morphine were required to achieved pain control than of ketorolac. • Patients in morphine group achieved pain control quicker, but ketorolac group sustained pain relief longer. • Sedation ↓ ketorolac group.	Jadad score: 3	B
Mendel et al, 1995	• Randomized controlled trial	• 54 patients; • Age: 4.2 ± 2.13 yr • Outpatient strabismus surgery	• Ketorolac 0.9 mg/kg • Fentanyl 1 microgram/kg, • Saline placebo diluted to a total volume of 2 mls	• Patients in the placebo and ketorolac group had a significantly lower rate of emesis compared with the fentanyl group. • Post-operative pain scores and the need for rescue medication did not differ among the groups. • No bleeding complications were noted.	Jadad score: 1	B
Munro et al, 1994	• Double-blind • Prospective, randomized study	• 42 patients, • Age: 5.2 (2-9)[+] yr • Outpatient strabismus surgery	• Ketorolac 0.75 mg/kg • Morphine 0.1 mg/kg and metoclopramide 0.15 mg/kg IV	• No difference in pain behavior scores or recovery times. • Significant increase in nausea and vomiting in the morphine group.	Jadad score: 2	B
Munro et al, 2002	• Prospective, randomized double-blind placebo-controlled study	• 35 patients, • Age: 14 ± 1.25 yr • Posterior spinal fusion surgery	Ketorolac 0.5 mg/kg or Normal Saline 5 ml	• No difference in post-operative blood loss or transfusion requirements, puritis, N&V or constipation. • Ketorolac group tolerated movement on POD one.	Jadad score: 3	B

[+] Age presented in mode (range)

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Table A-4. Characteristics of Included Studies Cont.

Park et al, 2000	• Double-blind randomized study	• 24 patients, • Age: 5.95 (4-11.5) yr[&] • Ureteral re-implantation surgery	• Ketorolac 0.5 mg/kg • Normal Saline to equal volume	• Ketorolac is effective in reducing the frequency and severity of postoperative bladder spasms.	Jadad score: 3	B
Purday et al, 1996	• Randomized, double-blind, prospective study	• 120 patients • Age: 4 (2-10)yr[$] • Dental restorative surgery	• Ketorolac 0.75 mg/kg • Ketorolac 1.0 mg/kg • Ketorolac 1.5 mg/kg • Morphine 0.1 mg/kg IV	• No differences detected in the OPS at 15 or 30 mins between morphine and ketorolac groups. • No difference in post-operative bleeding or rescue medication needs. • Post-operative vomiting was more frequent in the morphine group than any of the ketorolac groups	Jadad Score: 2	B
Romsing, 1998	• Randomized, double-blind, placebo-controlled study	• 60 patients, • Age: 9.3 ± 3.4 yr • Tonsillectomy	• Ketorolac 1 mg/kg • Placebo	• Pain scores, vomiting and acetaminophen dosing were significantly lower in ketorolac group. • No difference in pain scores or post-operative hemorrhage.	Jadad Score:3	B
Shende, 1999	• Randomized, double- blind study	• 52 patients • Age: 7±3.6 yr • Strabismus surgery	• Ketorolac 0.9 mg/kg • Pethidine 0.5 mg/kg	• Recovery scores, pain scores and post operative analgesic requirements were similar in both groups. • N&V occurred more often in pethidine than ketorolac group	Jadad Score: 1	B

[&] Age presented in mean (range)
[$] Age presented in median (range)

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Table A-4. Characteristics of Included Studies Cont.

Sutters et al, 1999	• Prospective, randomized double blind, placebo controlled study	• 68 patients, • Age; Avg 12.6 yr • Orthopedic surgery	• Ketorolac 1 mg/kg loading dose with 0.5 mg/kg q6h • Placebo	• Increased pain control and decreased opioid need with ketorolac	Jadad Score: 3	A
Watcha, 1992	• Randomized, double-blind placebo controlled study	• 95 patients • Age: 8.9 ± 3.7 yr	• Ketorolac 0.9 mg/kg • Morphine 0.1 mg/kg • Normal saline	• No statistically significant difference in pain scores when comparing morphine and ketorolac. • Placebo group had significantly higher pain scores and more frequent rescue dosing. • Ketorolac group had less emesis than morphine group.	Jadad Score: 3	B

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Figure A-4.

Objective Pain Scale – Ketorolac vs. Opioids- First Reported Pain Scores

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 01 Self Reported Pain Scales - Ketorolac vs Opioids
Outcome: 01 First Reported Pain Score - OPS

Study or sub-category	Ketorolac N	Ketorolac Mean (SD)	Opioid N	Opioid Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
01 All surgeries							
Watcha, 1992	32	1.00(2.25)	31	2.00(2.25)		24.11	-1.00 [-2.11, 0.11]
Mendel et al, 1995	18	2.70(1.70)	18	3.20(3.00)		19.00	-0.50 [-2.09, 1.09]
Purday et al, 1996	90	1.67(2.04)	30	0.00(1.75)		27.96	1.67 [0.92, 2.42]
Shende, 1999	26	2.00(1.27)	26	1.96(1.14)		28.93	0.04 [-0.62, 0.70]
Subtotal (95% CI)	166		105			100.00	0.13 [-1.07, 1.32]
Test for heterogeneity: $Chi^2 = 19.35$, df = 3 (P = 0.0002), $I^2 = 84.5\%$							
Test for overall effect: Z = 0.21 (P = 0.84)							
02 Day Surgery Patients							
Mendel et al, 1995	18	2.70(1.70)	18	3.20(3.00)		25.03	-0.50 [-2.09, 1.09]
Purday et al, 1996	90	1.67(2.04)	30	0.00(1.75)		36.85	1.67 [0.92, 2.42]
Shende, 1999	26	2.00(1.27)	26	1.96(1.14)		38.12	0.04 [-0.62, 0.70]
Subtotal (95% CI)	134		74			100.00	0.50 [-0.80, 1.80]
Test for heterogeneity: $Chi^2 = 12.33$, df = 2 (P = 0.002), $I^2 = 83.8\%$							
Test for overall effect: Z = 0.75 (P = 0.45)							
03 Inpatients							
Watcha, 1992	32	1.00(2.25)	31	2.00(2.25)		100.00	-1.00 [-2.11, 0.11]
Subtotal (95% CI)	32		31			100.00	-1.00 [-2.11, 0.11]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 1.76 (P = 0.08)							

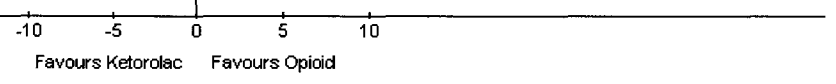

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Figure A-5.

Self Reported Pain Scales – Ketorolac vs. Opioids

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 03 Observational Pain Scales - Ketorolac vs Opioids
Outcome: 01 Oucher Scale

Study or sub-category	Ketorolac n/N	Placebo n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
01 Acheived Pain Relief					
Lieh-Lai, 1999	31/54	21/48		0.00	1.73 [0.79, 3.80]
Subtotal (95% CI)	54	48		0.00	1.73 [0.79, 3.80]
Total events: 31 (Ketorolac), 21 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 1.37 (P = 0.17)					
Total (95% CI)	54	48		0.00	1.73 [0.79, 3.80]
Total events: 31 (Ketorolac), 21 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 1.37 (P = 0.17)					

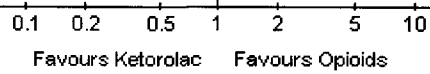

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Figure A-6.

Rescue Dosing – Ketorolac vs. Opioids - Patients Requiring Post-Operative PRN Medications

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 04 Rescue Dosing - Ketorolac vs Opioids
Outcome: 01 Patients requiring post-operative PRN medications for pain

Study or sub-category	Ketorolac n/N	Opioids n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 All surgeries					
Maunuksela, 1992	42/61	22/31		30.35	0.97 [0.73, 1.29]
Munro et al, 1994	3/21	5/21		2.02	0.60 [0.16, 2.20]
Gunter, 1995	21/49	13/47		9.81	1.55 [0.88, 2.72]
Mendel et al, 1995	13/18	12/18		15.49	1.08 [0.70, 1.67]
Purday et al, 1996	51/90	9/30		9.46	1.89 [1.06, 3.36]
Lieh-Lai, 1999	31/54	30/48		25.52	0.92 [0.67, 1.26]
Shende, 1999	10/26	11/26		7.33	0.91 [0.47, 1.76]
Subtotal (95% CI)	319	221		100.00	1.08 [0.88, 1.33]
Total events: 171 (Ketorolac), 102 (Opioids)					
Test for heterogeneity: Chi² = 8.22, df = 6 (P = 0.22), I² = 27.0%					
Test for overall effect: Z = 0.74 (P = 0.46)					
02 Tonsillectomies with/without adenoidectomy					
Gunter, 1995	21/49	13/47		50.39	1.55 [0.88, 2.72]
Keidan et al, 2004	10/25	18/32		49.61	0.71 [0.40, 1.26]
Subtotal (95% CI)	74	79		100.00	1.05 [0.49, 2.26]
Total events: 31 (Ketorolac), 31 (Opioids)					
Test for heterogeneity: Chi² = 3.66, df = 1 (P = 0.06), I² = 72.7%					
Test for overall effect: Z = 0.13 (P = 0.90)					
03 Strabismus Repair					
Munro et al, 1994	3/21	5/21		8.13	0.60 [0.16, 2.20]
Mendel et al, 1995	13/18	12/18		62.36	1.08 [0.70, 1.67]
Shende, 1999	10/26	11/26		29.52	0.91 [0.47, 1.76]
Subtotal (95% CI)	65	65		100.00	0.99 [0.70, 1.40]
Total events: 26 (Ketorolac), 28 (Opioids)					
Test for heterogeneity: Chi² = 0.92, df = 2 (P = 0.63), I² = 0%					
Test for overall effect: Z = 0.07 (P = 0.95)					

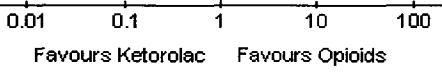

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Figure A-7.

Rescue Dosing – Ketorolac vs. Opioids -Inpatients vs. Day Surgery Patients

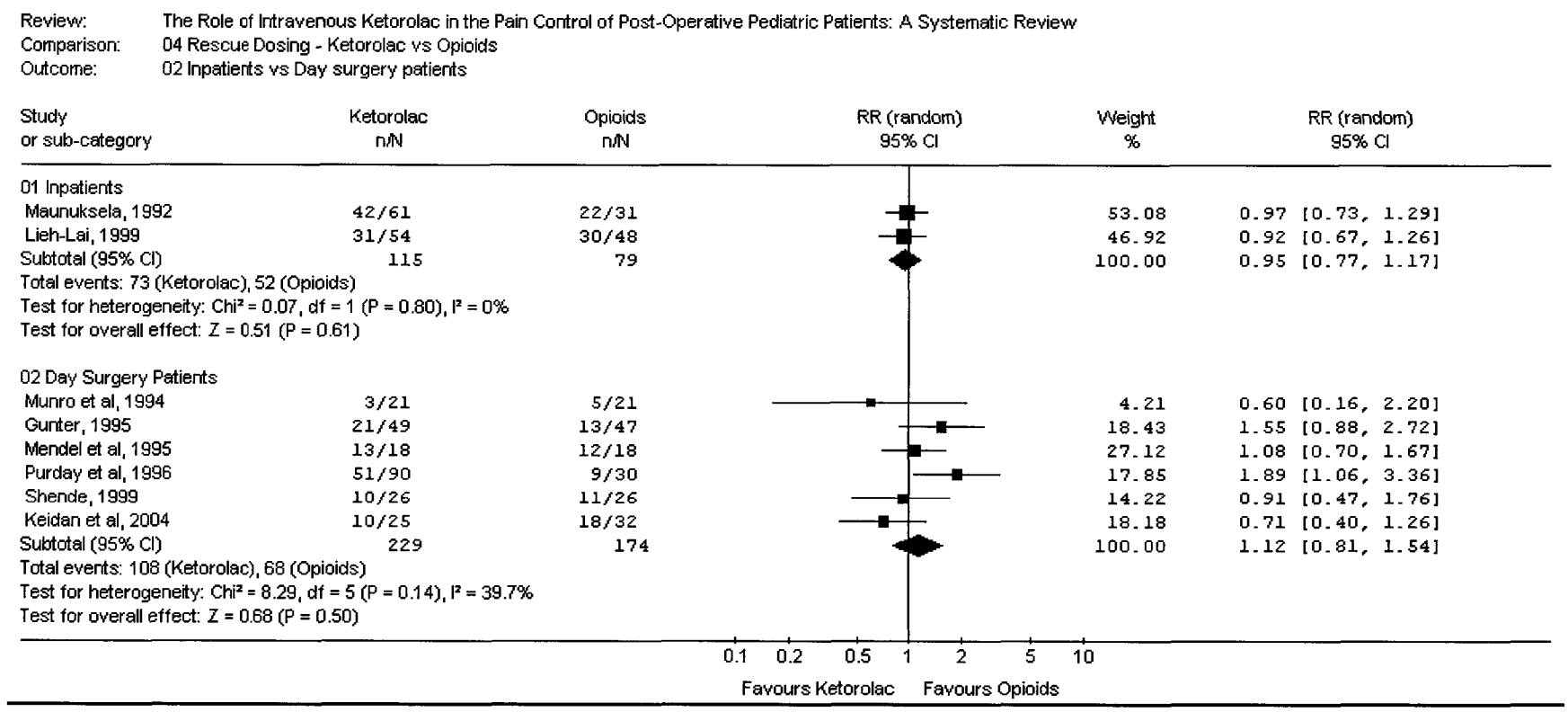

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Figure A-8.

Rescue Dosing – Ketorolac vs. Opioids - High Dose Ketorolac vs. Low Dose Ketorolac

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 04 Rescue Dosing - Ketorolac vs Opioids
Outcome: 03 High dose vs Low dose Ketorolac

Study or sub-category	Ketorolac n/N	Opioids n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
01 High dose Ketorolac (>=0.6 mg/kg/dose)					
Munro et al, 1994	3/21	5/21		4.89	0.60 [0.16, 2.20]
Gunter, 1995	21/49	13/47		12.97	1.55 [0.88, 2.72]
Mendel et al, 1995	13/18	12/18		11.73	1.08 [0.70, 1.67]
Purday et al, 1996	51/90	9/30		13.19	1.89 [1.06, 3.36]
Lieh-Lai, 1999	31/54	30/48		31.04	0.92 [0.67, 1.26]
Shende, 1999	10/26	11/26		10.75	0.91 [0.47, 1.76]
Keidan et al, 2004	10/25	18/32		15.43	0.71 [0.40, 1.26]
Subtotal (95% CI)	283	222		100.00	1.10 [0.90, 1.34]
Total events: 139 (Ketorolac), 98 (Opioids)					
Test for heterogeneity: $Chi^2 = 9.46$, df = 6 (P = 0.15), $I^2 = 36.5\%$					
Test for overall effect: Z = 0.93 (P = 0.35)					
02 Low dose Ketorolac (<=0.5 mg/kg/dose)					
Maunuksela, 1992	42/61	22/31		100.00	0.97 [0.73, 1.29]
Subtotal (95% CI)	61	31		100.00	0.97 [0.73, 1.29]
Total events: 42 (Ketorolac), 22 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.21 (P = 0.83)					

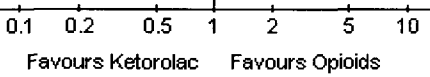

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Figure A-9.

Rescue Dosing – Ketorolac vs. Opioids - Pre/Intra-Operative Dosing vs. Post-Operative Dosing

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 04 Rescue Dosing - Ketorolac vs Opioids
Outcome: 04 Intra/Pre operative dosing va Post-operative dosing

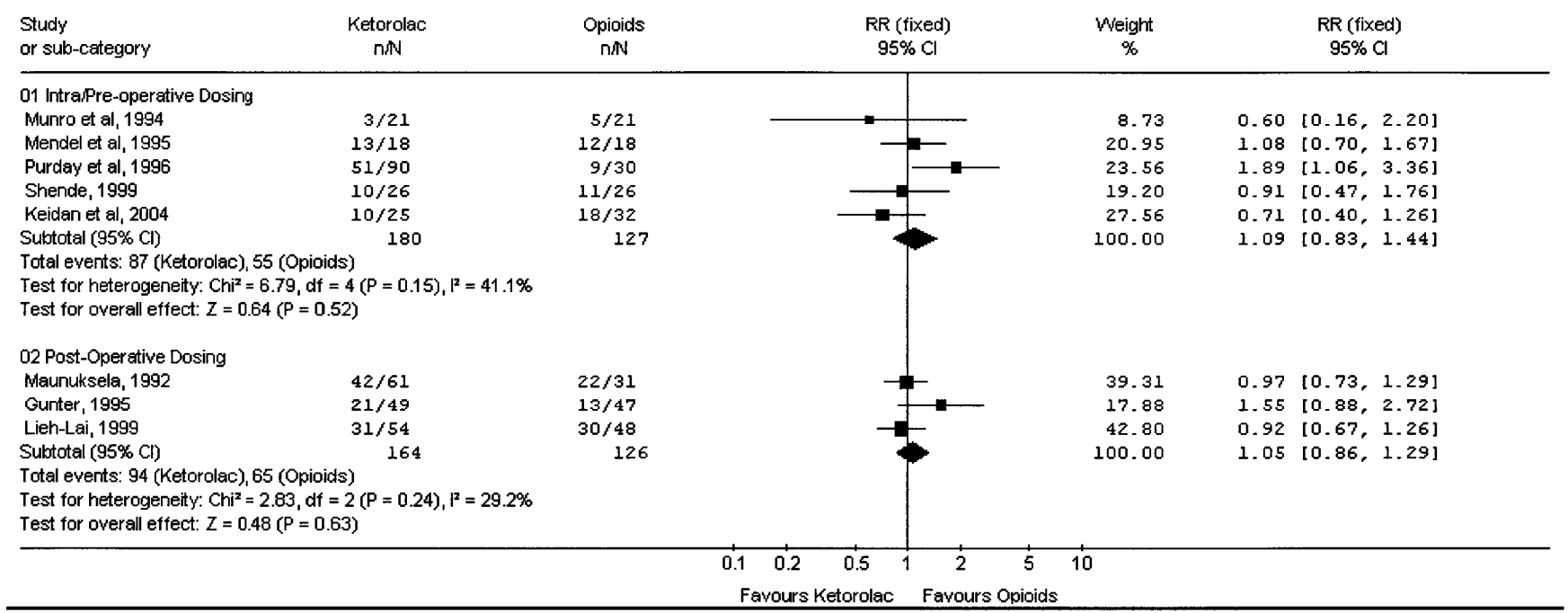

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Figure A-10.

Time to Discharge – Ketorolac vs. Opioids -Discharge from Recovery Room or PARR

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 06 Time to Discharge - Ketorolac vs Opioids
Outcome: 01 Discharge from Recovery Room or PARR (mins)

Study or sub-category	Ketorolac N	Ketorolac Mean (SD)	Opioids N	Opioids Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 All surgeries							
Watcha, 1992	32	35.80(10.70)	31	39.70(19.40)		37.90	-3.90 [-11.67, 3.87]
Gunter, 1995	49	71.00(31.00)	47	69.00(33.00)		13.93	2.00 [-10.82, 14.82]
Purday et al, 1996	90	46.33(13.94)	30	47.00(17.50)		48.17	-0.67 [-7.56, 6.22]
Subtotal (95% CI)	171		108			100.00	-1.52 [-6.31, 3.26]
Test for heterogeneity: Chi² = 0.71, df = 2 (P = 0.70), I² = 0%							
Test for overall effect: Z = 0.62 (P = 0.53)							
02 Tonsillecotmy with/without adenoidectomy							
Gunter, 1995	49	71.00(31.00)	47	69.00(33.00)		100.00	2.00 [-10.82, 14.82]
Subtotal (95% CI)	49		47			100.00	2.00 [-10.82, 14.82]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.31 (P = 0.76)							

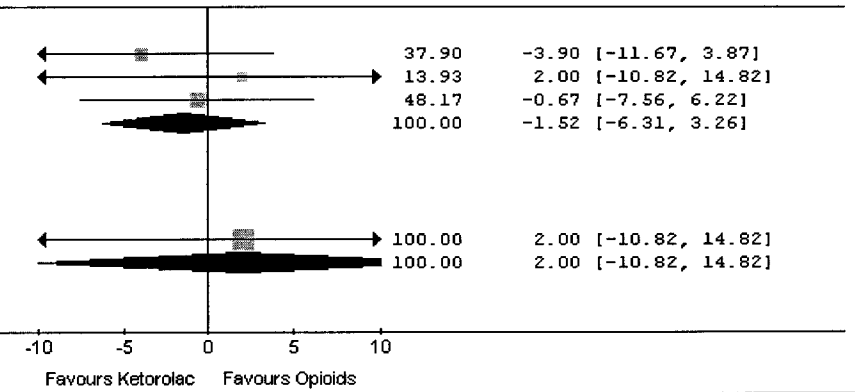

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Figure A-11.

Time to Discharge – Ketorolac vs. Opioids - Discharge from Hospital

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 06 Time to Discharge - Ketorolac vs Opioids
Outcome: 02 Discharge from Hospital (mins)

Study or sub-category	Ketorolac N	Ketorolac Mean (SD)	Opioids N	Opioids Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
01 All surgeries							
Munro et al, 1994	21	107.00(23.00)	21	116.00(28.00)		37.84	-9.00 [-24.50, 6.50]
Gunter, 1995	49	226.00(109.00)	47	229.00(70.00)		9.41	-3.00 [-39.50, 33.50]
Mendel et al, 1995	18	160.00(48.00)	18	134.00(38.00)		14.85	26.00 [-2.28, 54.28]
Purday et al, 1996	90	76.67(23.37)	3	75.00(13.00)		37.89	1.67 [-13.81, 17.15]
Gupta et al, 2005	35	7200.00(17280.00)	35	5760.00(6840.00)		0.00	1440.00 [-4716.94, 7596.94]
Subtotal (95% CI)	213		124			100.00	0.81 [-10.89, 12.51]
Test for heterogeneity: Chi² = 4.82, df = 4 (P = 0.31), I² = 17.1%							
Test for overall effect: Z = 0.14 (P = 0.89)							
02 Tonsillectomy with/without adenoidectomy							
Gunter, 1995	49	226.00(109.00)	47	229.00(70.00)		100.00	-3.00 [-39.50, 33.50]
Subtotal (95% CI)	49		47			100.00	-3.00 [-39.50, 33.50]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.16 (P = 0.87)							
03 Cardiac surgery							
Gupta et al, 2005	35	7200.00(17280.00)	35	5760.00(6840.00)		100.00	1440.00 [-4716.94, 7596.94]
Subtotal (95% CI)	35		35			100.00	1440.00 [-4716.94, 7596.94]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.46 (P = 0.65)							
04 Stribismus Repair							
Munro et al, 1994	21	107.00(23.00)	21	116.00(28.00)		71.82	-9.00 [-24.50, 6.50]
Mendel et al, 1995	18	160.00(48.00)	18	134.00(38.00)		28.18	26.00 [-2.28, 54.28]
Subtotal (95% CI)	39		39			100.00	6.42 [-27.64, 40.47]
Test for heterogeneity: Chi² = 4.52, df = 1 (P = 0.03), I² = 77.9%							
Test for overall effect: Z = 0.37 (P = 0.71)							

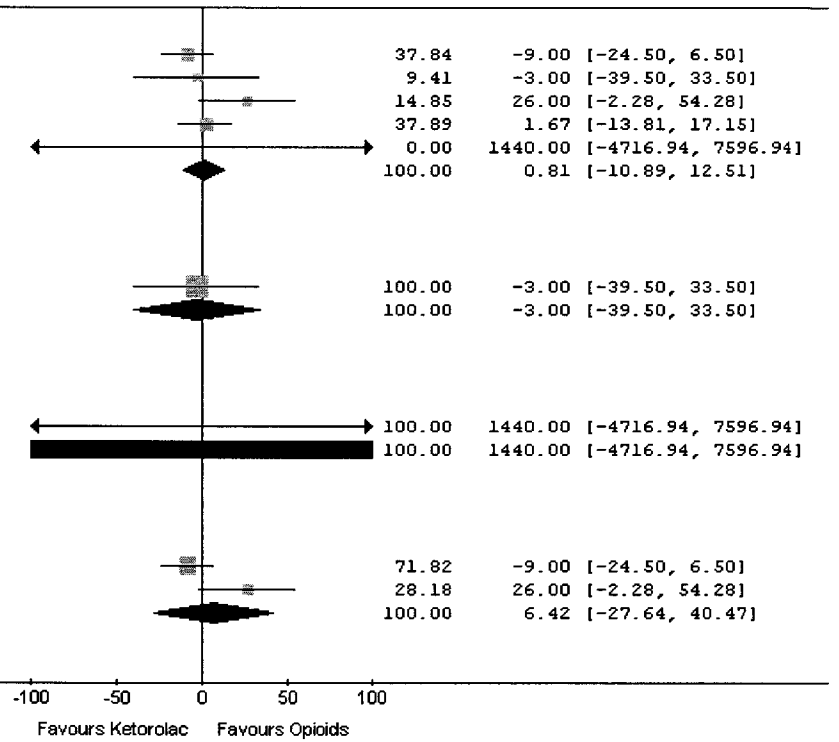

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Figure A-12.

Time to Discharge – Ketorolac vs. Opioids - Inpatients vs. Day Surgery Patients

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 06 Time to Discharge - Ketorolac vs Opioids
Outcome: 03 Daysurgery patients vs Inpatients

Study or sub-category	N	Ketorolac Mean (SD)	N	Opioids Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 Day Surgery Patients							
Munro et al, 1994	21	107.00(23.00)	21	116.00(28.00)		40.28	-9.00 [-24.50, 6.50]
Gunter, 1995	49	226.00(109.00)	47	229.00(70.00)		7.26	-3.00 [-39.50, 33.50]
Mendel et al, 1995	18	160.00(48.00)	18	134.00(38.00)		12.10	26.00 [-2.28, 54.28]
Purday et al, 1996	90	76.67(23.37)	3	75.00(13.00)		40.36	1.67 [-13.81, 17.15]
Subtotal (95% CI)	178		89			100.00	-0.02 [-9.86, 9.81]
Test for heterogeneity: Chi² = 4.61, df = 3 (P = 0.20), I² = 35.0%							
Test for overall effect: Z = 0.00 (P = 1.00)							
02 Inpatients							
Gupta et al, 2005	35	7200.00(17280.00)	35	5760.00(6840.00)		100.00	1440.00 [-4716.94, 7596.94]
Subtotal (95% CI)	35		35			100.00	1440.00 [-4716.94, 7596.94]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 0.46 (P = 0.65)							

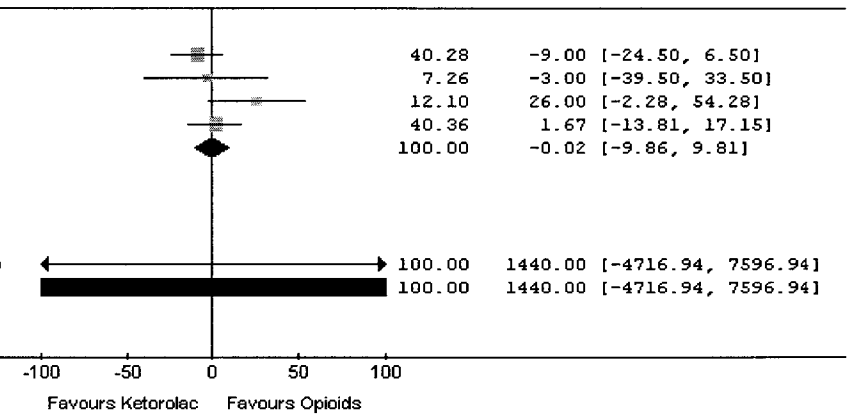

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Figure A-13.

Nausea and Vomiting – Ketorolac vs. Opioids - Had Any Post-Operative Nausea and Vomiting

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 08 N&V- Ketorolac vs Opioids
Outcome: 01 Had any N&V post-operativly

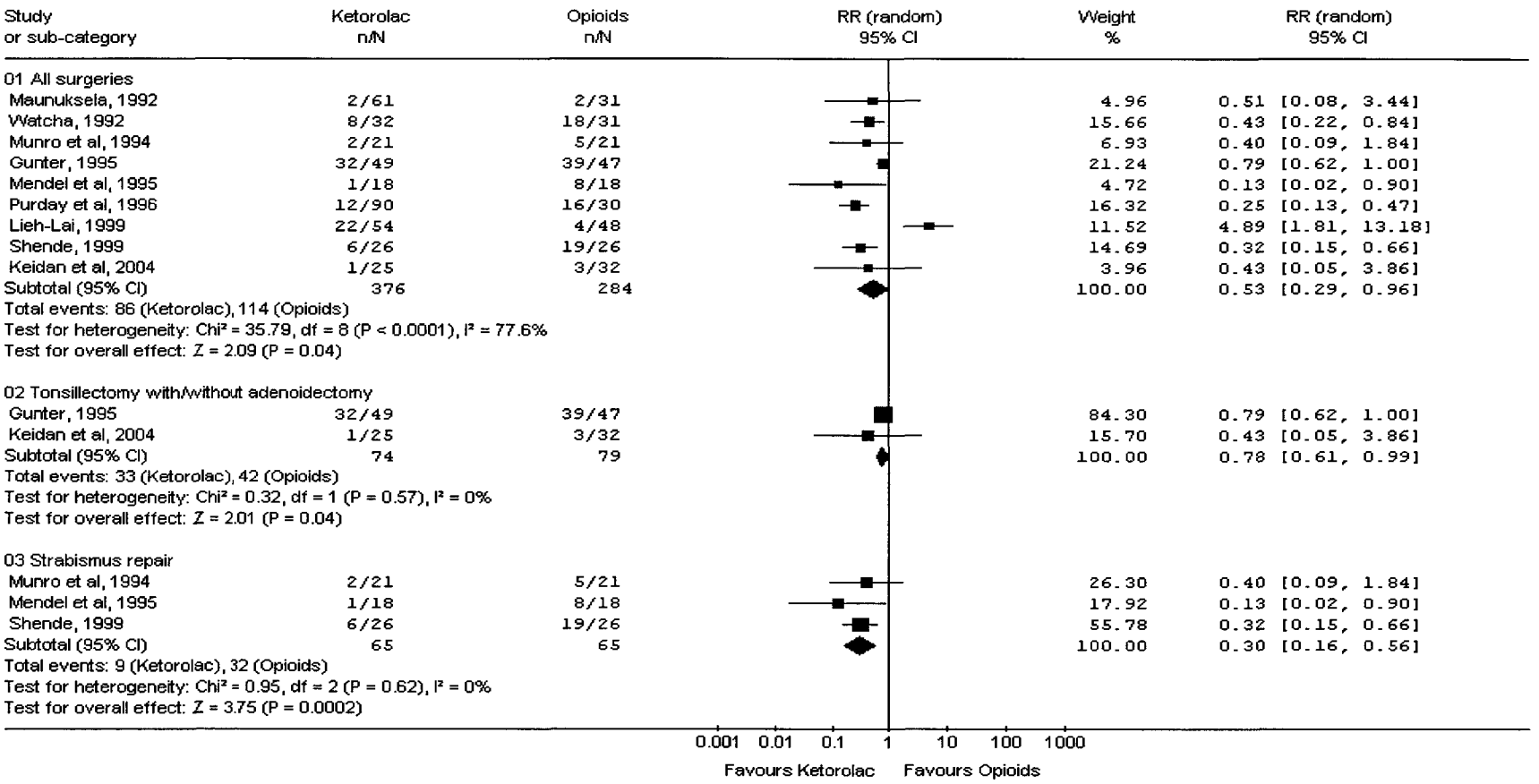

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Figure A-14.

Nausea and Vomiting – Ketorolac vs. Opioids - Day Surgery Patients vs. Inpatients

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 08 N&V- Ketorolac vs Opioids
Outcome: 02 Day surgery patients vs Inpatients

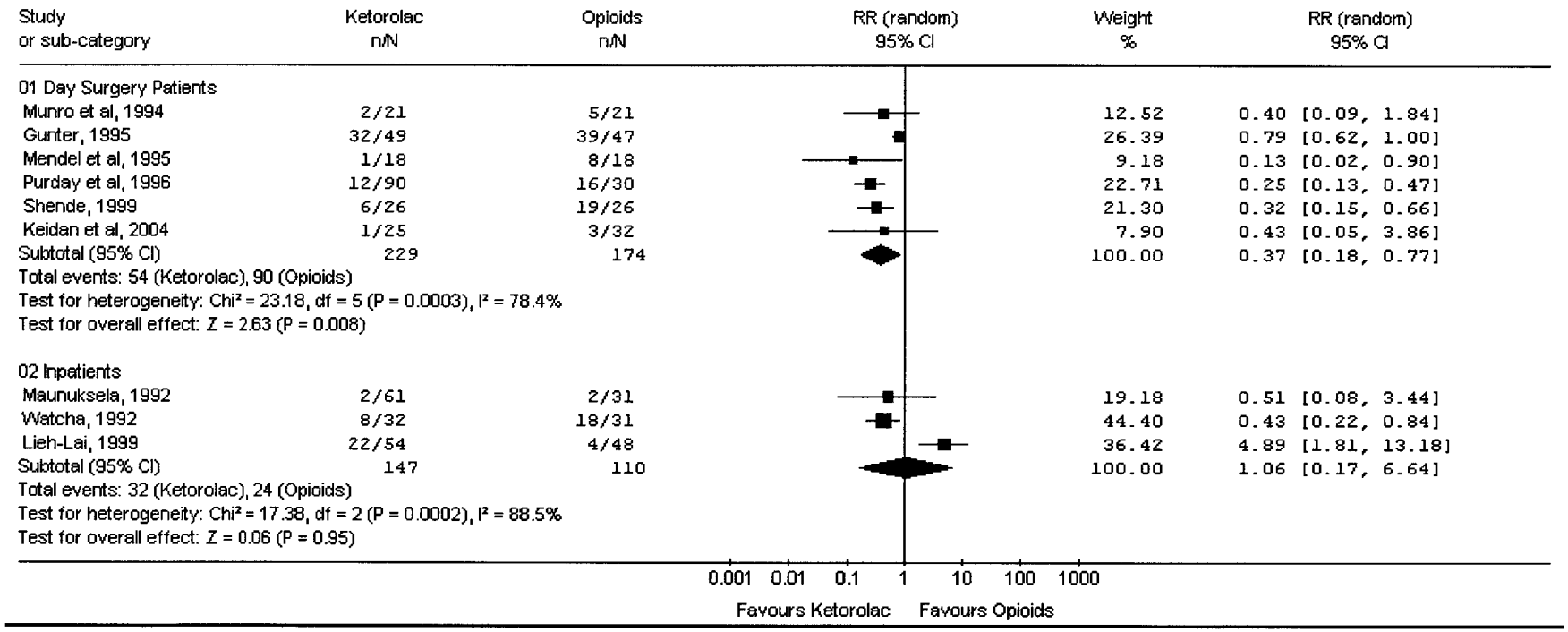

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Figure A-15.

Nausea and Vomiting – Ketorolac vs. Opioids - High Dose Ketorolac vs. Low Dose Ketorolac

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 08 N&V- Ketorolac vs Opioids
Outcome: 03 High dose Keotorlac vs Low dose Ketorolac

Study or sub-category	Ketorolac n/N	Opioids n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 High dose Ketorolac (>=0.6 mg/kg/dose)					
Watcha, 1992	8/32	18/31		15.79	0.43 [0.22, 0.84]
Munro et al, 1994	2/21	5/21		8.92	0.40 [0.09, 1.84]
Gunter, 1995	32/49	39/47		18.81	0.79 [0.62, 1.00]
Mendel et al, 1995	1/18	8/18		6.54	0.13 [0.02, 0.90]
Purday et al, 1996	12/90	16/30		16.19	0.25 [0.13, 0.47]
Lieh-Lai, 1999	22/54	4/48		12.95	4.89 [1.81, 13.18]
Shende, 1999	6/26	19/26		15.18	0.32 [0.15, 0.66]
Keidan et al, 2004	1/25	3/32		5.63	0.43 [0.05, 3.86]
Subtotal (95% CI)	315	253		100.00	0.53 [0.28, 0.99]
Total events: 84 (Ketorolac), 112 (Opioids)					
Test for heterogeneity: Chi² = 35.72, df = 7 (P < 0.00001), I² = 80.4%					
Test for overall effect: Z = 1.98 (P = 0.05)					
02 Low dose ketorolac (<=0.5 mg/kg/dose)					
Maunuksela, 1992	2/61	2/31		100.00	0.51 [0.08, 3.44]
Subtotal (95% CI)	61	31		100.00	0.51 [0.08, 3.44]
Total events: 2 (Ketorolac), 2 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					

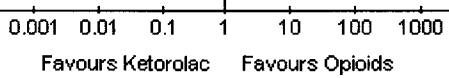

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Figure A-16.

Bleeding – Ketorolac vs. Opioids - Any Post-Operative Bleeding Event

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 10 Bleeding Events- Ketorolac vs Opioids
Outcome: 01 Any bleeding event

Study or sub-category	Ketorolac n/N	Opioids n/N	Peto OR 95% CI	Weight %	Peto OR 95% CI
01 All surgeries					
Watcha, 1992	0/32	0/31			Not estimable
Gunter, 1995	8/49	8/47		87.23	0.95 [0.33, 2.77]
Mendel et al, 1995	0/18	0/18			Not estimable
Purday et al, 1996	0/90	0/30			Not estimable
Lieh-Lai, 1999	0/54	0/48			Not estimable
Shende, 1999	0/26	0/26			Not estimable
Keidan et al, 2004	0/25	0/32			Not estimable
Gupta et al, 2005	1/35	1/35		12.77	1.00 [0.06, 16.32]
Subtotal (95% CI)	329	267		100.00	0.96 [0.35, 2.60]
Total events: 9 (Ketorolac), 9 (Opioids)					
Test for heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.97), $I^2 = 0\%$					
Test for overall effect: Z = 0.08 (P = 0.93)					
02 Tonsillecotmy with/without adenoidectomy					
Gunter, 1995	8/49	8/47		100.00	0.95 [0.33, 2.77]
Keidan et al, 2004	0/25	0/32			Not estimable
Subtotal (95% CI)	74	79		100.00	0.95 [0.33, 2.77]
Total events: 8 (Ketorolac), 8 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.09 (P = 0.93)					
03 Strabismus repair					
Mendel et al, 1995	0/18	0/18			Not estimable
Shende, 1999	0/26	0/26			Not estimable
Subtotal (95% CI)	44	44			Not estimable
Total events: 0 (Ketorolac), 0 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
04 Cardiac surgery					
Gupta et al, 2005	1/35	1/35		100.00	1.00 [0.06, 16.32]
Subtotal (95% CI)	35	35		100.00	1.00 [0.06, 16.32]
Total events: 1 (Ketorolac), 1 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.00 (P = 1.00)					

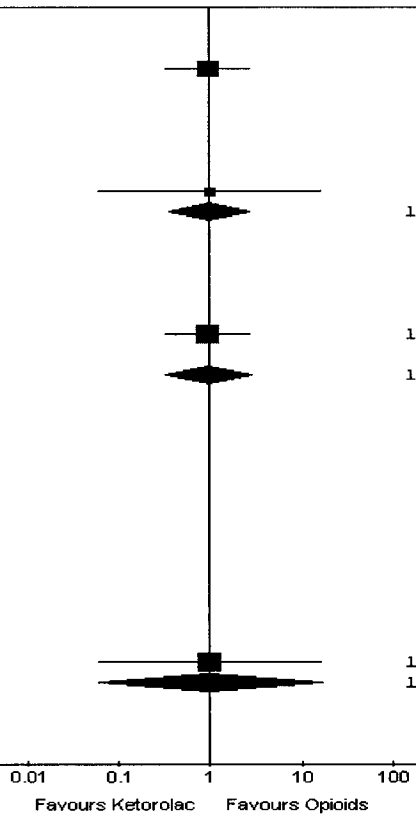

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Figure A-17.

Bleeding – Ketorolac vs. Opioids - Milliliters of Blood Loss in Drains

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 10 Bleeding Events- Ketorolac vs Opioids
Outcome: 02 Drain blood loss (mls)

Study or sub-category	N	Ketorolac Mean (SD)	N	Opioids Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Gupta et al, 2005	35	13.30(4.50)	35	16.50(5.25)		100.00	-3.20 [-5.49, -0.91]
Total (95% CI)	35		35			100.00	-3.20 [-5.49, -0.91]

Test for heterogeneity: not applicable
Test for overall effect: Z = 2.74 (P = 0.006)

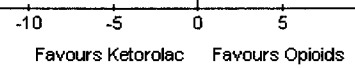

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Figure A-18.

Bleeding – Ketorolac vs. Opioids - Bleeding Time

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 10 Bleeding Events- Ketorolac vs Opioids
Outcome: 03 Bleeding time

Study or sub-category	Ketorolac N	Ketorolac Mean (SD)	Opioids N	Opioids Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Lieh-Lai, 1999	54	6.00(4.00)	48	6.00(6.00)		100.00	0.00 [-2.00, 2.00]
Total (95% CI)	54		48			100.00	0.00 [-2.00, 2.00]

Test for heterogeneity: not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

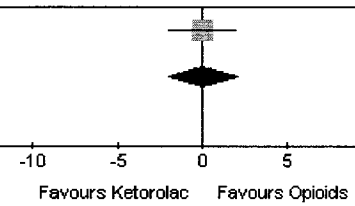

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Figure A-19.

Bleeding – Ketorolac vs. Opioids - Requiring Readmission to Hospital or Re-operation Due to Bleeding

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 10 Bleeding Events- Ketorolac vs Opioids
Outcome: 04 Readmission/Reoperation

Study or sub-category	Ketorolac n/N	Opioids n/N	Peto OR 95% CI	Weight %	Peto OR 95% CI
Watcha, 1992	0/32	0/31			Not estimable
Gunter, 1995	3/49	1/47		100.00	2.69 [0.37, 19.73]
Total (95% CI)	81	78		100.00	2.69 [0.37, 19.73]

Total events: 3 (Ketorolac), 1 (Opioids)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.97 (P = 0.33)

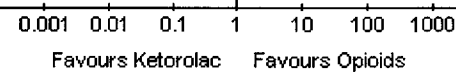

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Figure A-20.

Bleeding – Ketorolac vs. Opioids - Inpatients vs. Outpatients

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 10 Bleeding Events- Ketorolac vs Opioids
Outcome: 05 Inpatients vs Day surgery patients

Study or sub-category	Ketorolac n/N	Opioids n/N	Peto OR 95% CI	Weight %	Peto OR 95% CI
01 Inpatients					
Watcha, 1992	0/32	0/31			Not estimable
Lieh-Lai, 1999	0/54	0/48			Not estimable
Gupta et al, 2005	1/35	1/35		12.77	1.00 [0.06, 16.32]
Subtotal (95% CI)	121	114		12.77	1.00 [0.06, 16.32]
Total events: 1 (Ketorolac), 1 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.00 (P = 1.00)					
02 Daysurgery Patients					
Gunter, 1995	8/49	8/47		87.23	0.95 [0.33, 2.77]
Mendel et al, 1995	0/18	0/18			Not estimable
Purday et al, 1996	0/90	0/30			Not estimable
Shende, 1999	0/26	0/26			Not estimable
Keidan et al, 2004	0/25	0/32			Not estimable
Subtotal (95% CI)	208	153		87.23	0.95 [0.33, 2.77]
Total events: 8 (Ketorolac), 8 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.09 (P = 0.93)					
Total (95% CI)	329	267		100.00	0.96 [0.35, 2.60]
Total events: 9 (Ketorolac), 9 (Opioids)					
Test for heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.97), $I^2 = 0\%$					
Test for overall effect: Z = 0.08 (P = 0.93)					

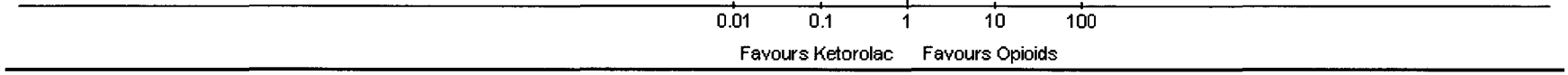

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Figure A-21.

Bleeding – Ketorolac vs. Opioids - High Dose Ketorolac vs. Low Dose Ketorolac

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 10 Bleeding Events- Ketorolac vs Opioids
Outcome: 06 High dose Ketorolac vs Low dose Ketorolac

Study or sub-category	Ketorolac n/N	Opioids n/N	Peto OR 95% CI	Weight %	Peto OR 95% CI
01 High dose Ketorolac (>=0.6 mg/kg/dose)					
Watcha, 1992	0/32	0/31			Not estimable
Gunter, 1995	8/49	8/47		87.23	0.95 [0.33, 2.77]
Mendel et al, 1995	0/18	0/18			Not estimable
Purday et al, 1996	0/90	0/30			Not estimable
Lieh-Lai, 1999	0/54	0/48			Not estimable
Shende, 1999	0/26	0/26			Not estimable
Keidan et al, 2004	0/25	0/32			Not estimable
Subtotal (95% CI)	294	232		87.23	0.95 [0.33, 2.77]
Total events: 8 (Ketorolac), 8 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.09 (P = 0.93)					
02 Low dose Ketorolac (<=0.5 mg/kg/dose)					
Gupta et al, 2005	1/35	1/35		12.77	1.00 [0.06, 16.32]
Subtotal (95% CI)	35	35		12.77	1.00 [0.06, 16.32]
Total events: 1 (Ketorolac), 1 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.00 (P = 1.00)					
Total (95% CI)	329	267		100.00	0.96 [0.35, 2.60]
Total events: 9 (Ketorolac), 9 (Opioids)					
Test for heterogeneity: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%					
Test for overall effect: Z = 0.08 (P = 0.93)					

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Figure A-22.

Bleeding – Ketorolac vs. Opioids - Dose Duration >24 Hours vs. Dose Duration <24 Hours

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 10 Bleeding Events- Ketorolac vs Opioids
Outcome: 07 > 24 hours doing vs <24 hour dosing

Study or sub-category	Ketorolac n/N	Opioids n/N	Peto OR 95% CI	Weight %	Peto OR 95% CI
01 >24 hour dosing					
Gupta et al, 2005	1/35	1/35		12.77	1.00 [0.06, 16.32]
Subtotal (95% CI)	35	35		12.77	1.00 [0.06, 16.32]
Total events: 1 (Ketorolac), 1 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.00 (P = 1.00)					
02 <24 hour dosing					
Watcha, 1992	0/32	0/31			Not estimable
Gunter, 1995	8/49	8/47		87.23	0.95 [0.33, 2.77]
Mendel et al, 1995	0/18	0/18			Not estimable
Purday et al, 1996	0/90	0/30			Not estimable
Lieh-Lai, 1999	0/54	0/48			Not estimable
Shende, 1999	0/26	0/26			Not estimable
Keidan et al, 2004	0/25	0/32			Not estimable
Subtotal (95% CI)	294	232		87.23	0.95 [0.33, 2.77]
Total events: 8 (Ketorolac), 8 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.09 (P = 0.93)					
Total (95% CI)	329	267		100.00	0.96 [0.35, 2.60]
Total events: 9 (Ketorolac), 9 (Opioids)					
Test for heterogeneity: Chi² = 0.00, df = 1 (P = 0.97), I² = 0%					
Test for overall effect: Z = 0.08 (P = 0.93)					

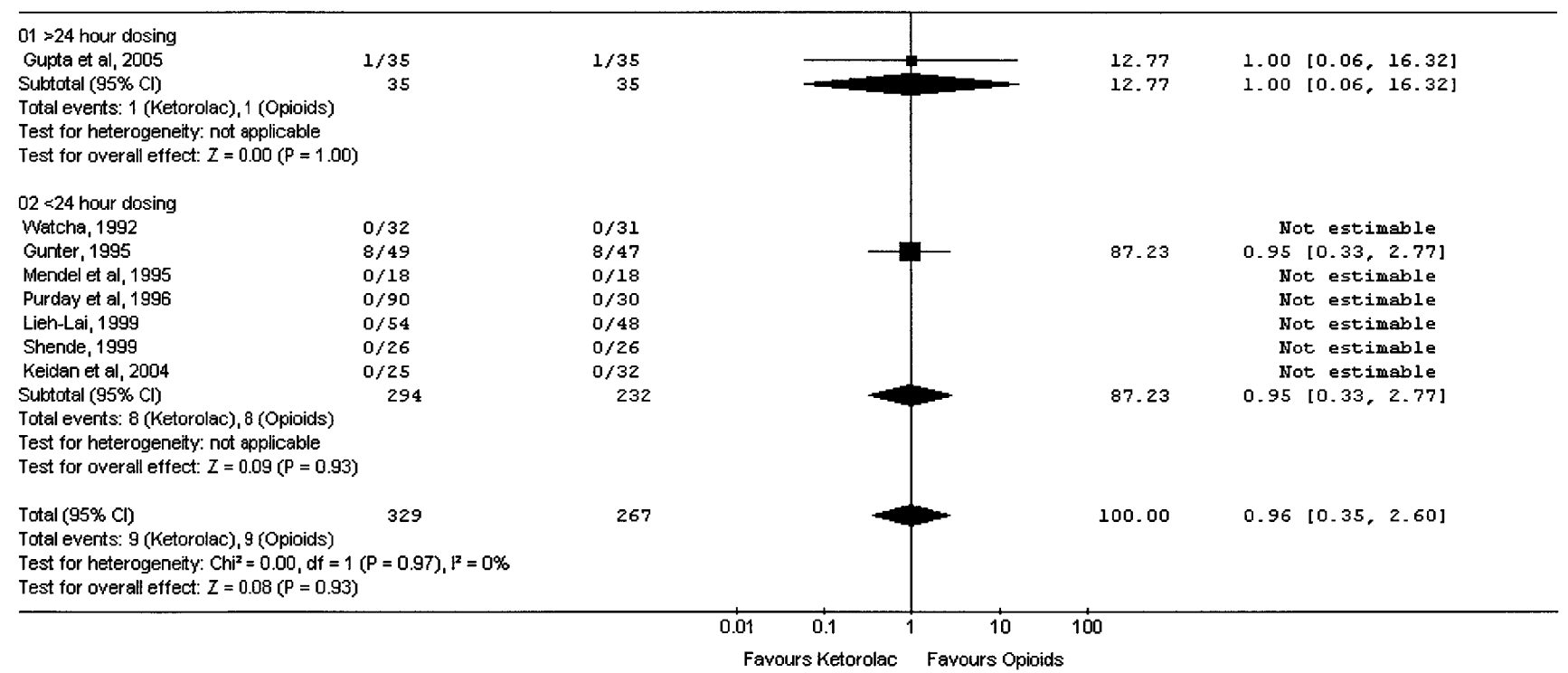

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Figure A-23.

Bleeding - Gunter et al. Study

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 10 Bleeding Events- Ketorolac vs Opioids
Outcome: 08 Gunter et al Study

Study or sub-category	Ketorolac n/N	Opioids n/N	Peto OR 95% CI	Weight %	Peto OR 95% CI
01 Bleeding events <24 hours					
Gunter, 1995	13/49	2/47		100.00	5.32 [1.78, 15.93]
Subtotal (95% CI)	49	47		100.00	5.32 [1.78, 15.93]
Total events: 13 (Ketorolac), 2 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 2.99 (P = 0.003)					
02 Bleeding events >24 hours					
Gunter, 1995	7/49	12/47		100.00	0.50 [0.18, 1.35]
Subtotal (95% CI)	49	47		100.00	0.50 [0.18, 1.35]
Total events: 7 (Ketorolac), 12 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 1.38 (P = 0.17)					
03 Post-operative bleeding requiring re-operation					
Gunter, 1995	2/49	1/47		100.00	1.89 [0.19, 18.66]
Subtotal (95% CI)	49	47		100.00	1.89 [0.19, 18.66]
Total events: 2 (Ketorolac), 1 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.55 (P = 0.58)					
09 Any Bleeding					
Gunter, 1995	8/49	8/47		100.00	0.95 [0.33, 2.77]
Subtotal (95% CI)	49	47		100.00	0.95 [0.33, 2.77]
Total events: 8 (Ketorolac), 8 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.09 (P = 0.93)					
10 Major bleeding					
Gunter, 1995	6/49	5/47		100.00	1.17 [0.34, 4.08]
Subtotal (95% CI)	49	47		100.00	1.17 [0.34, 4.08]
Total events: 6 (Ketorolac), 5 (Opioids)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 0.25 (P = 0.81)					

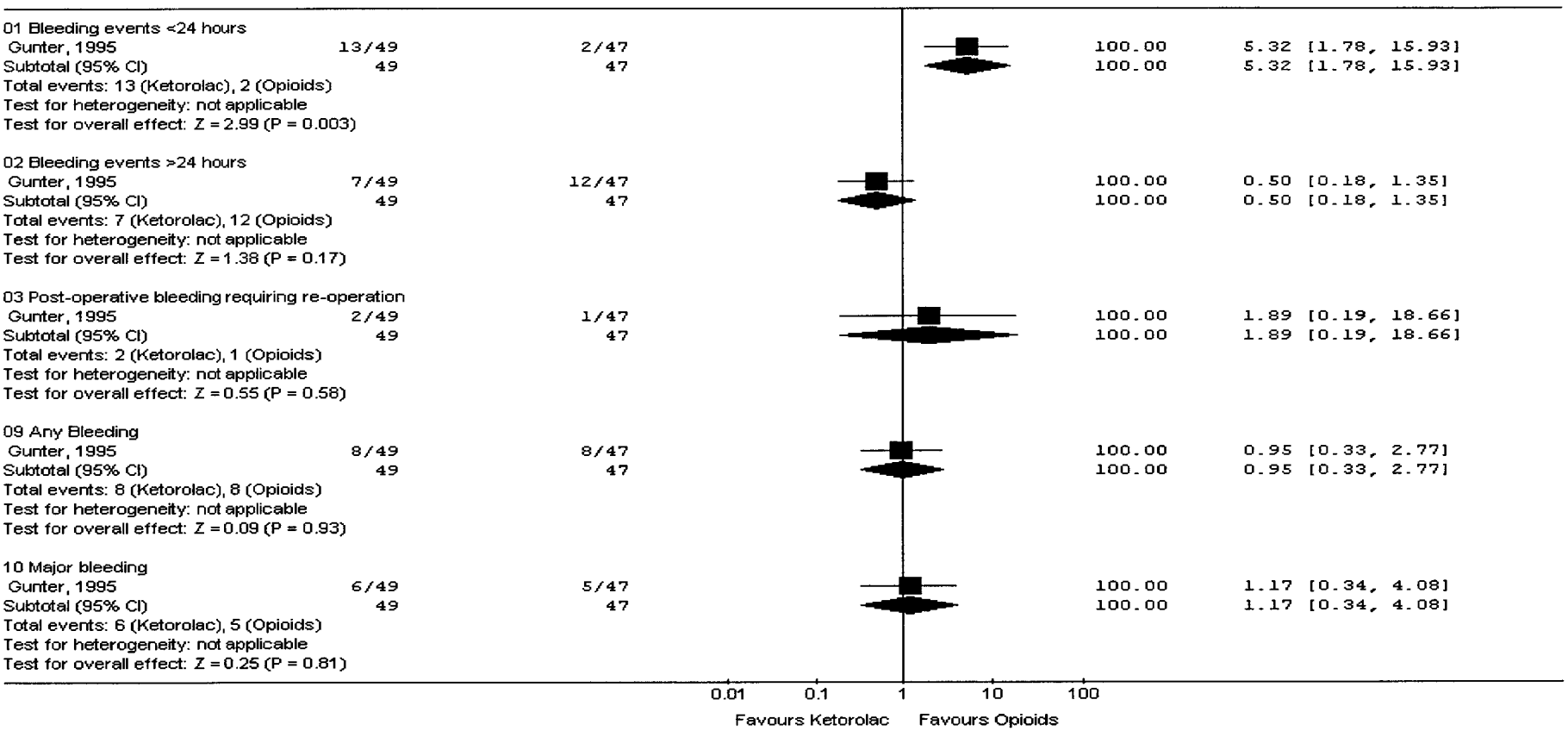

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Figure A-24.

Maladaptive Behaviors – Ketorolac vs. Opioids - Post-Operative Agitation

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 12 Post-operative maladaptive behaviors - Ketorolac vs Opioids
Outcome: 02 Aggitated

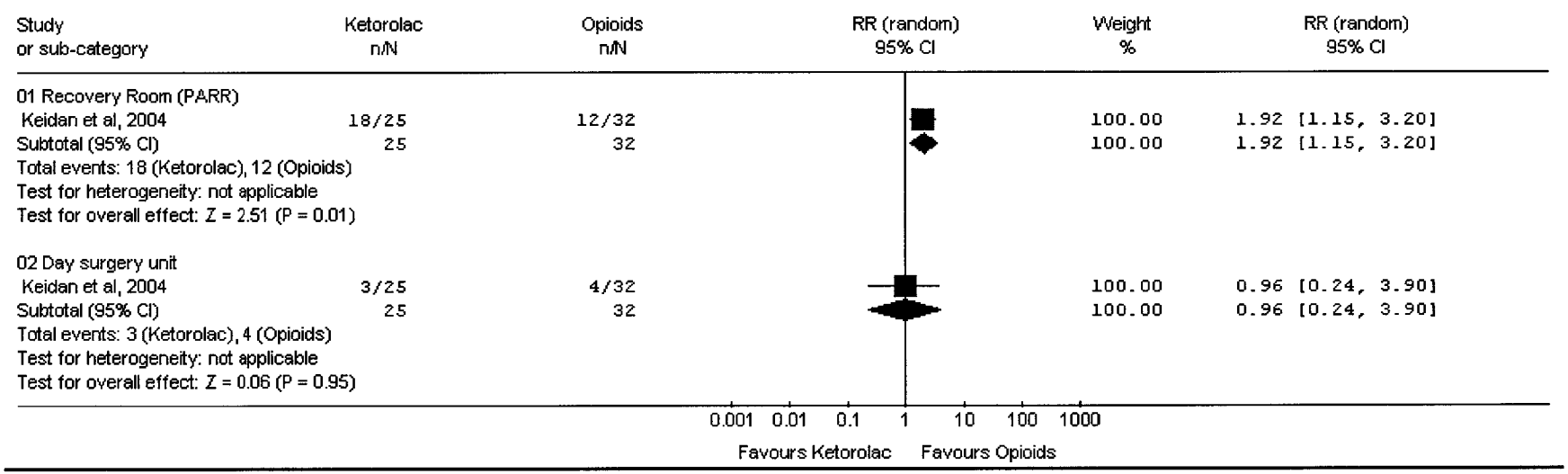

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Figure A-25.

Maladaptive Behaviors – Ketorolac vs. Opioids - Abnormal Nighttime Sleeping Pattern

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 12 Post-operative maladaptive behaviors - Ketorolac vs Opioids
Outcome: 03 Abnormal night time sleeping pattern

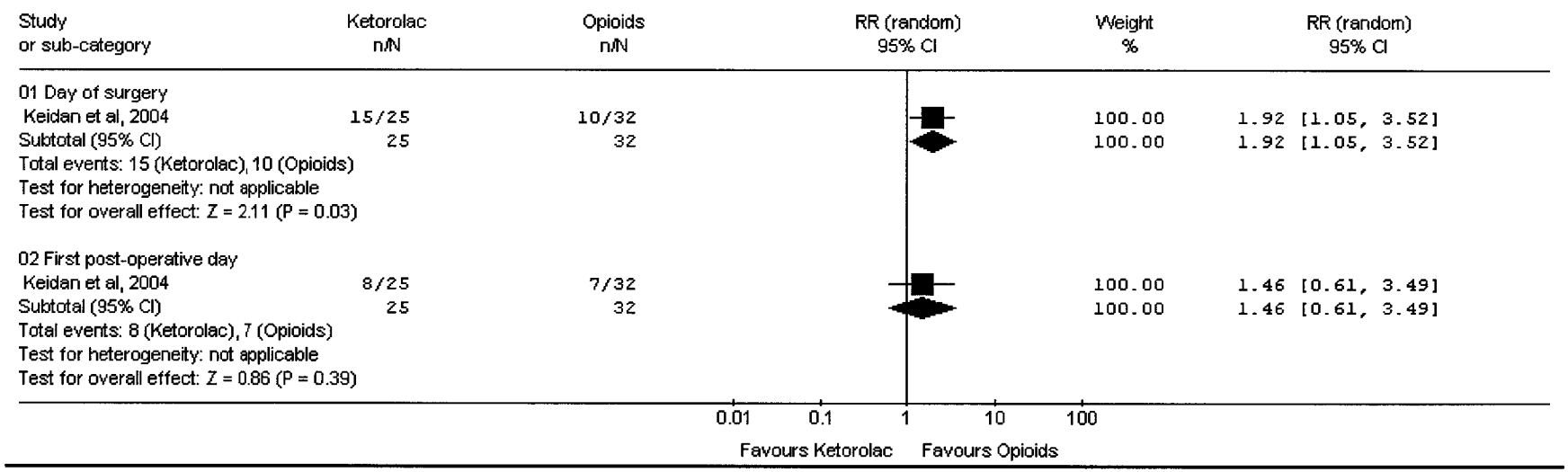

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Figure A-26.

Poker Chip Scale– Ketorolac vs. Placebo - First Reported Pain Score

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 02 Self Reported Pain Scales - Ketorolac vs Placebo
Outcome: 01 Poker Chip

Study or sub-category	N	Ketorolac Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 First Reported Pain Score							
Romsing, 1998	40	1.55(0.80)	20	2.30(0.90)		100.00	-0.75 [-1.22, -0.28]
Subtotal (95% CI)	40		20			100.00	-0.75 [-1.22, -0.28]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 3.16 (P = 0.002)							

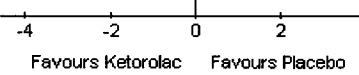

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Figure A-27.

Objective Pain Scale – Ketorolac vs. Placebo - First Reported Pain Scores

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 02 Self Reported Pain Scales - Ketorolac vs Placebo
Outcome: 02 OPS

Study or sub-category	Ketorolac N	Ketorolac Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
01 First Reported Pain Score							
Watcha, 1992	32	1.00(2.25)	32	4.00(2.25)		49.94	-3.00 [-4.10, -1.90]
Mendel et al, 1995	18	2.70(1.70)	18	2.20(1.60)		50.06	0.50 [-0.58, 1.58]
Subtotal (95% CI)	50		50			100.00	-1.25 [-4.68, 2.18]

Test for heterogeneity: $Chi^2 = 19.78$, df = 1 ($P < 0.00001$), $I^2 = 94.9\%$
Test for overall effect: Z = 0.71 (P = 0.48)

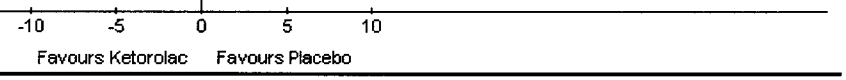

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Figure A-28.

Self Reported Pain Scales – Ketorolac vs. Placebo – Post-operative bladder spasms

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 02 Self Reported Pain Scales - Ketorolac vs Placebo
Outcome: 03 Bladder Spasms

Study or sub-category	Ketorolac n/N	Placebo n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI
Park et al, 2000	3/12	10/12		100.00	0.30 [0.11, 0.83]
Total (95% CI)	12	12		100.00	0.30 [0.11, 0.83]

Total events: 3 (Ketorolac), 10 (Placebo)
Test for heterogeneity: not applicable
Test for overall effect: Z = 2.33 (P = 0.02)

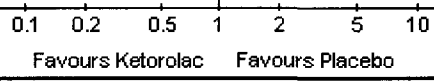

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Figure A-29.

Rescue Dosing – Ketorolac vs. Placebo - Patients Requiring Post-Operative PRN Medications

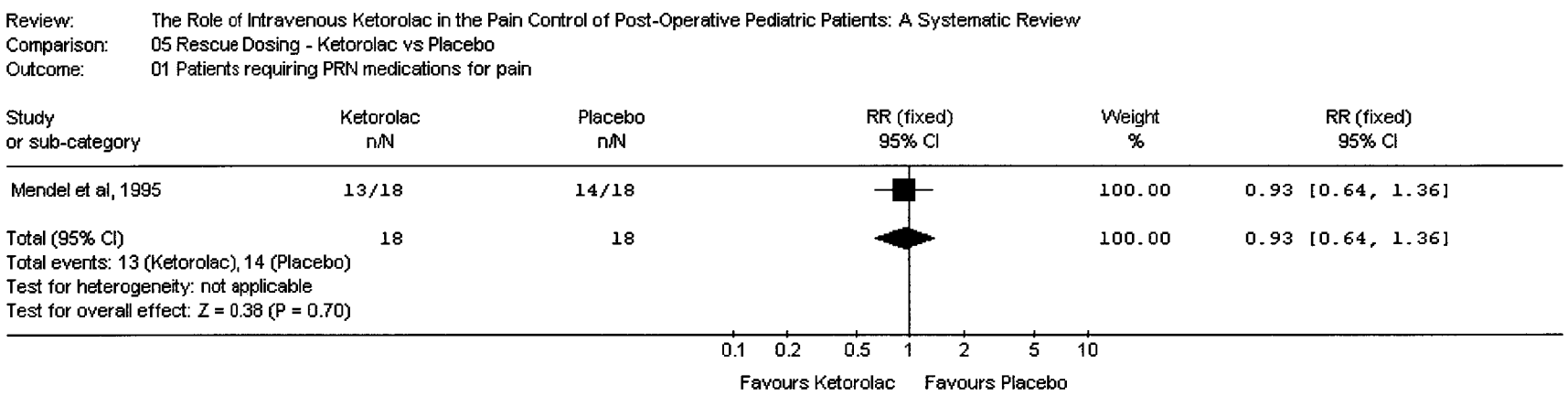

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Figure A-30.

Rescue Dosing – Ketorolac vs. Opioids - Micrograms of Fentanyl Required Post-Operatively for Pain Control

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 05 Rescue Dosing - Ketorolac vs Placebo
Outcome: 02 Micrograms of fentanyl required for pain control in recovery room

Study or sub-category	Ketorolac N	Ketorolac Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Sutters et al, 1999	36	19.71(31.46)	32	46.50(58.95)		100.00	-26.79 [-49.65, -3.93]
Total (95% CI)	36		32			100.00	-26.79 [-49.65, -3.93]

Test for heterogeneity: not applicable
Test for overall effect: Z = 2.30 (P = 0.02)

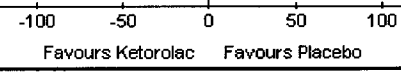

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Figure A-31.

Time to Discharge – Ketorolac vs. Placebo - Discharge from Recovery Room (PARR)

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 07 Time to Discharge - Ketorolac vs Placebo
Outcome: 01 Discharge from Recovery Room (PARR) (mins)

Study or sub-category	N	Ketorolac Mean (SD)	N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 All Surgeries							
Watcha, 1992	32	35.80(10.70)	32	46.00(14.20)		97.87	-10.20 [-16.36, -4.04]
Munro et al, 2002	20	301.00(63.00)	15	331.00(62.00)		2.13	-30.00 [-71.79, 11.79]
Subtotal (95% CI)	52		47			100.00	-10.62 [-16.72, -4.53]
Test for heterogeneity: $Chi^2 = 0.84$, df = 1 (P = 0.36), $I^2 = 0\%$							
Test for overall effect: Z = 3.42 (P = 0.0006)							
02 Orthopedic Surgery							
Munro et al, 2002	20	301.00(63.00)	15	331.00(62.00)		100.00	-30.00 [-71.79, 11.79]
Subtotal (95% CI)	20		15			100.00	-30.00 [-71.79, 11.79]
Test for heterogeneity: not applicable							
Test for overall effect: Z = 1.41 (P = 0.16)							

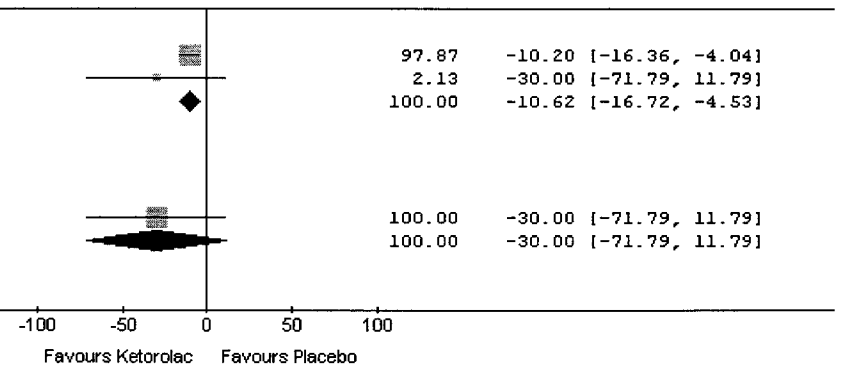

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Figure A-32.

Time to Discharge – Ketorolac vs. Placebo - Discharge from Hospital

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 07 Time to Discharge - Ketorolac vs Placebo
Outcome: 02 Discharge from Hospital (mins)

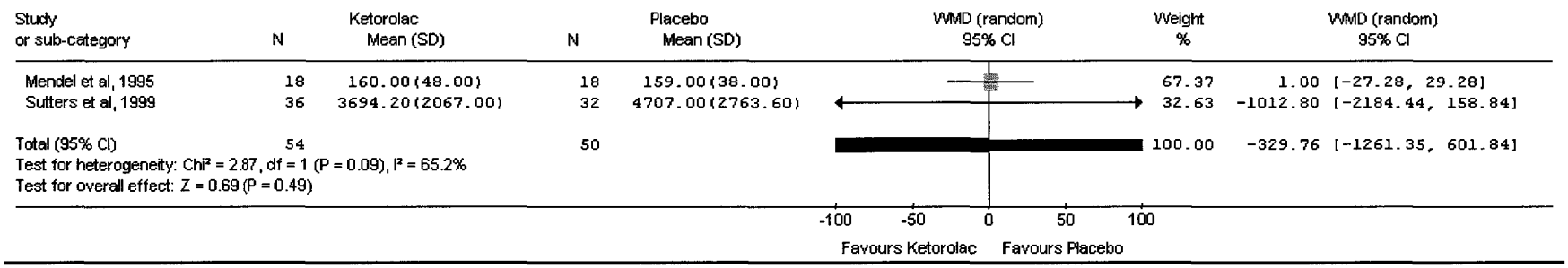

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Figure A-33.

Nausea and Vomiting – Ketorolac vs. Placebo - Any Post Operative Nausea and Vomiting

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 09 N&V - Ketorolac vs Placebo
Outcome: 01 Had any N&V post-operativly

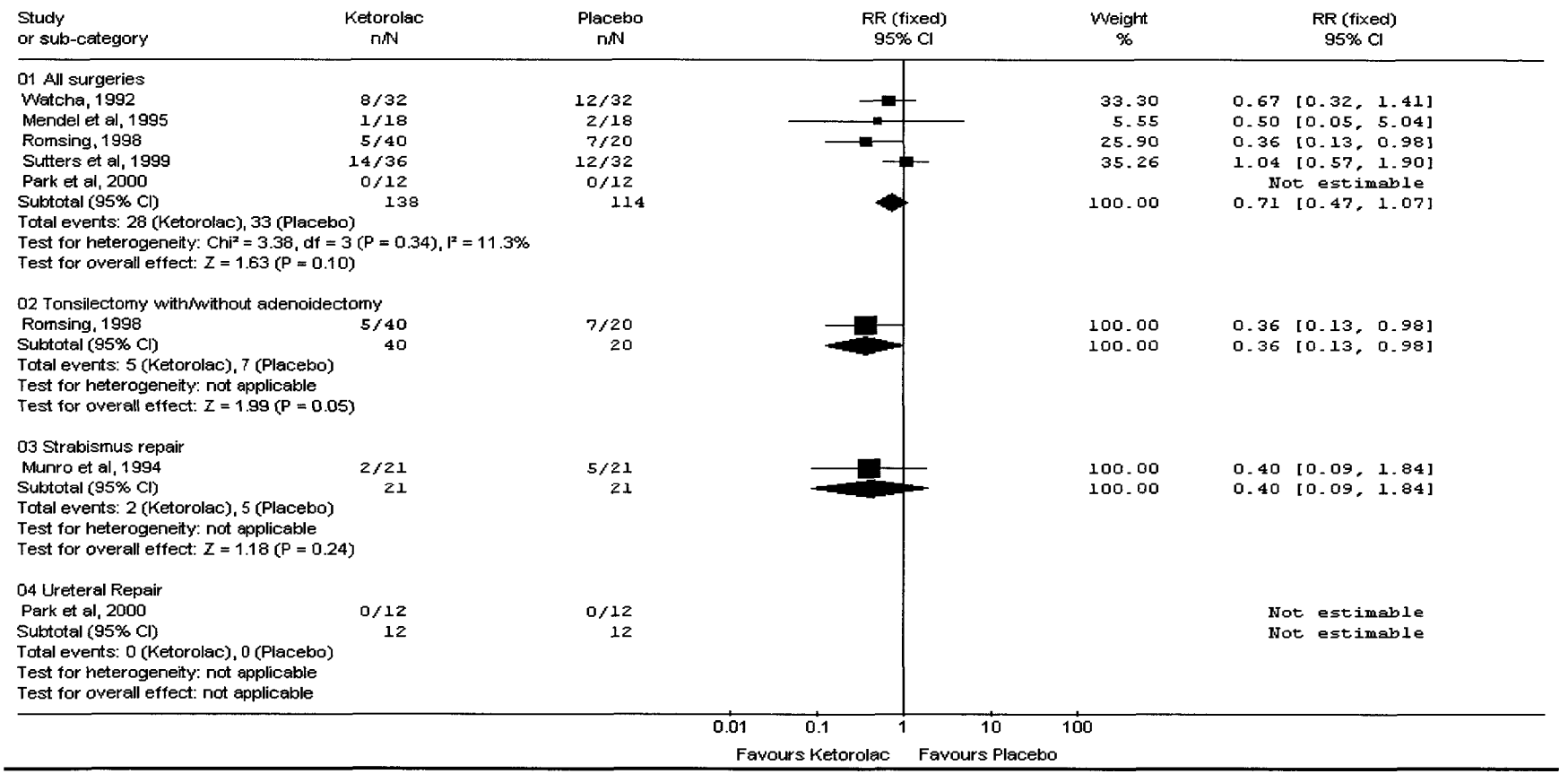

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Figure A-34.

Nausea and Vomiting – Ketorolac vs. Placebo - Day Surgery Patients vs. Inpatients

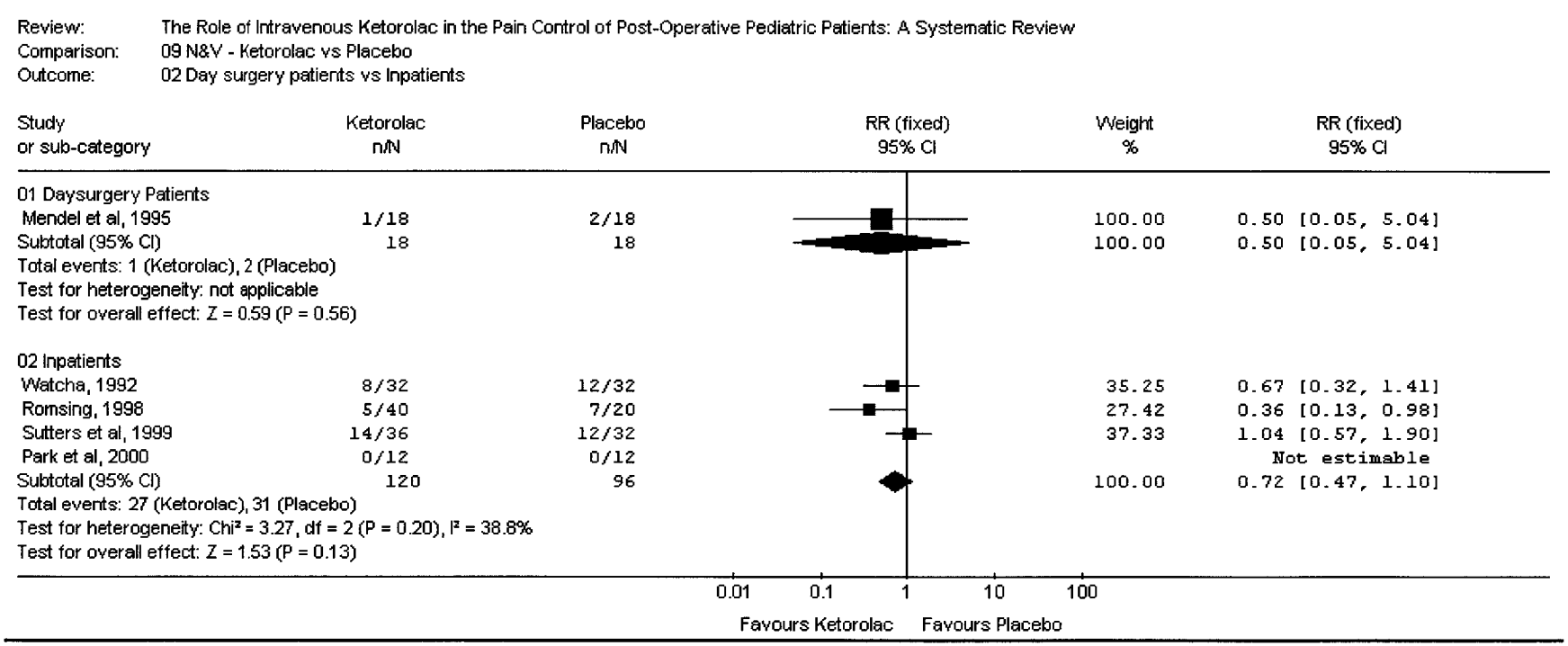

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Figure A-35.

Nausea and Vomiting – Ketorolac vs. Placebo - High Dose Ketorolac vs. Low Dose Ketorolac

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 09 N&V - Ketorolac vs Placebo
Outcome: 03 High dose Ketorolac vs Low dose Ketorolac

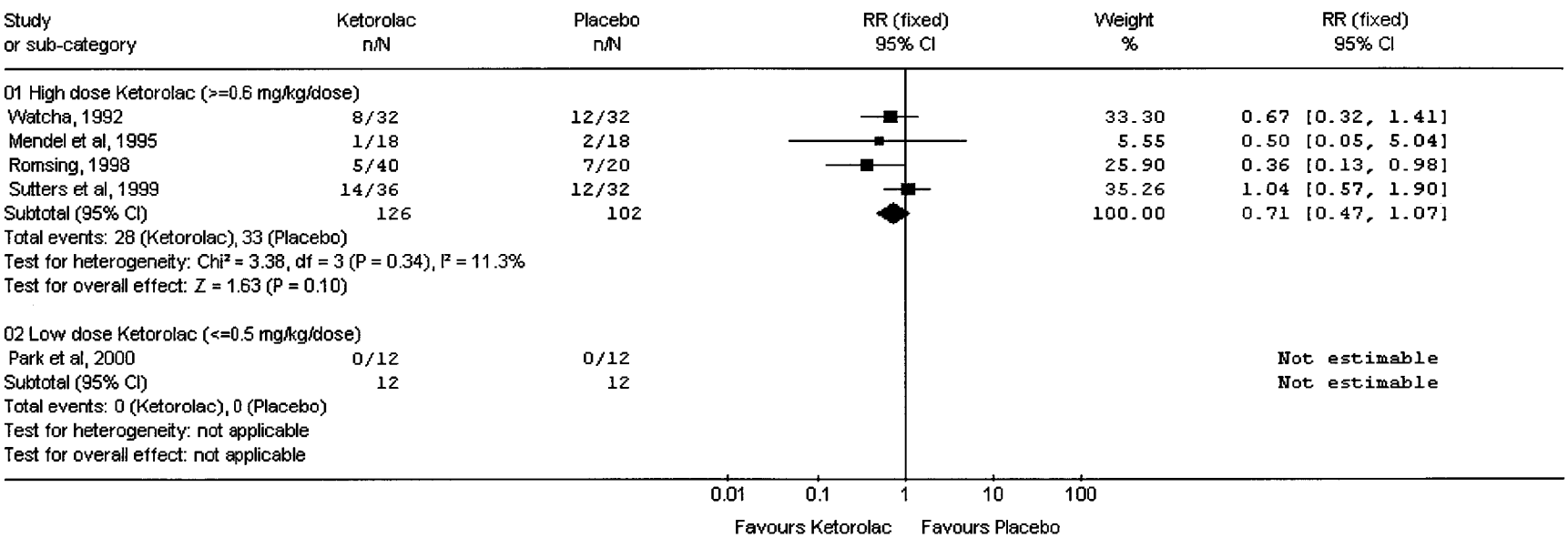

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Figure A-36.

Bleeding – Ketorolac vs. Placebo - Any Post-Operative Bleeding Event

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 11 Bleeding Events - Ketorolac vs Placebo
Outcome: 01 Any bleeding event

Study or sub-category	Ketorolac n/N	Placebo n/N	Peto OR 95% CI	Weight %	Peto OR 95% CI
01 All surgeries					
Watcha, 1992	0/32	1/32		7.72	0.14 [0.00, 6.82]
Mendel et al, 1995	0/18	0/18			Not estimable
Romsing, 1998	4/30	4/15		46.14	0.41 [0.08, 2.04]
Sutters et al, 1999	0/36	0/32			Not estimable
Park et al, 2000	0/12	0/12			Not estimable
Subtotal (95% CI)	128	109		53.86	0.35 [0.08, 1.54]
Total events: 4 (Ketorolac), 5 (Placebo)					
Test for heterogeneity: Chi² = 0.26, df = 1 (P = 0.61), I² = 0%					
Test for overall effect: Z = 1.39 (P = 0.17)					
02 Tonsillectomy with/without adenoidectomy					
Romsing, 1998	4/30	4/15		46.14	0.41 [0.08, 2.04]
Subtotal (95% CI)	30	15		46.14	0.41 [0.08, 2.04]
Total events: 4 (Ketorolac), 4 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect: Z = 1.09 (P = 0.28)					
03 Strabismus surgery					
Mendel et al, 1995	0/18	0/18			Not estimable
Subtotal (95% CI)	18	18			Not estimable
Total events: 0 (Ketorolac), 0 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
04 Ureteral reimplant					
Park et al, 2000	0/12	0/12			Not estimable
Subtotal (95% CI)	12	12			Not estimable
Total events: 0 (Ketorolac), 0 (Placebo)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	188	154		100.00	0.38 [0.13, 1.12]
Total events: 8 (Ketorolac), 9 (Placebo)					
Test for heterogeneity: Chi² = 0.28, df = 2 (P = 0.87), I² = 0%					
Test for overall effect: Z = 1.76 (P = 0.08)					

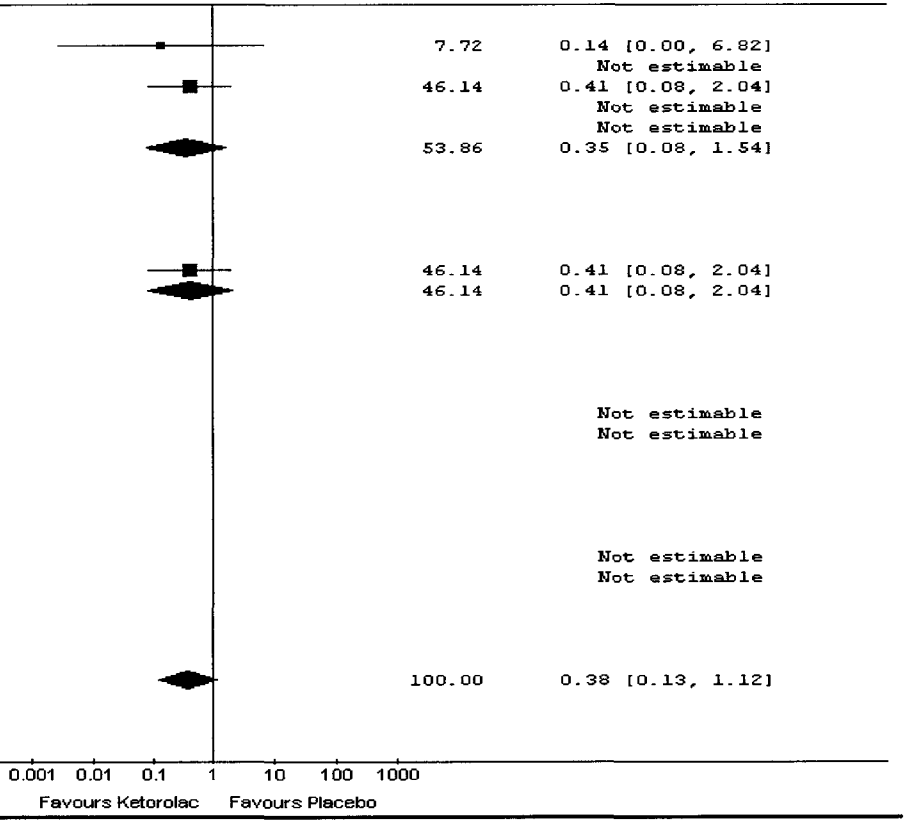

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Figure A-37.

Bleeding – Ketorolac vs. Placebo - Pre/Intra-operative Blood Loss

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 11 Bleeding Events - Ketorolac vs Placebo
Outcome: 02 Intraoperative blood loss

Study or sub-category	Ketorolac N	Ketorolac Mean (SD)	Placebo N	Placebo Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Romsing, 1998	40	3.15(2.50)	20	3.10(2.00)		100.00	0.05 [-1.12, 1.22]
Total (95% CI)	40		20			100.00	0.05 [-1.12, 1.22]

Test for heterogeneity: not applicable
Test for overall effect: Z = 0.08 (P = 0.93)

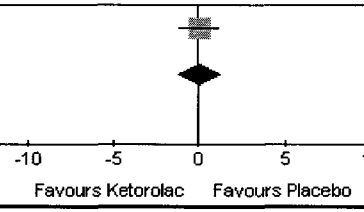

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Figure A-38.

Bleeding – Ketorolac vs. Placebo - Patients Requiring Post-Operative Blood Transfusions

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 11 Bleeding Events - Ketorolac vs Placebo
Outcome: 03 Postoperative transfusions

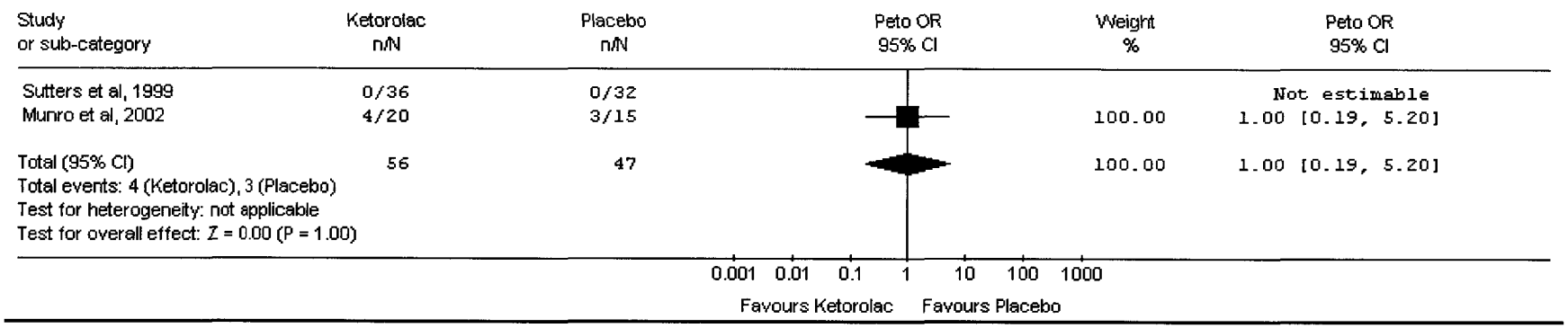

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Figure A-39.

Bleeding – Ketorolac vs. Placebo - Requiring Readmission to Hospital or Re-operation

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 11 Bleeding Events - Ketorolac vs Placebo
Outcome: 04 Readmission/Reoperation

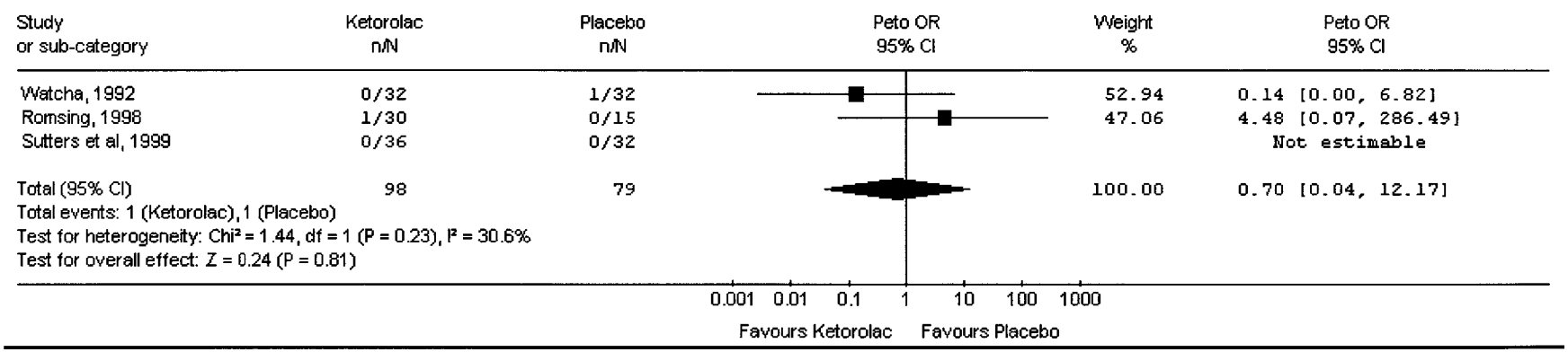

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Figure A-40.

Bleeding – Ketorolac vs. Placebo - Inpatients vs. Day Surgery

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 11 Bleeding Events - Ketorolac vs Placebo
Outcome: 05 Day surgery patients vs Inpatients

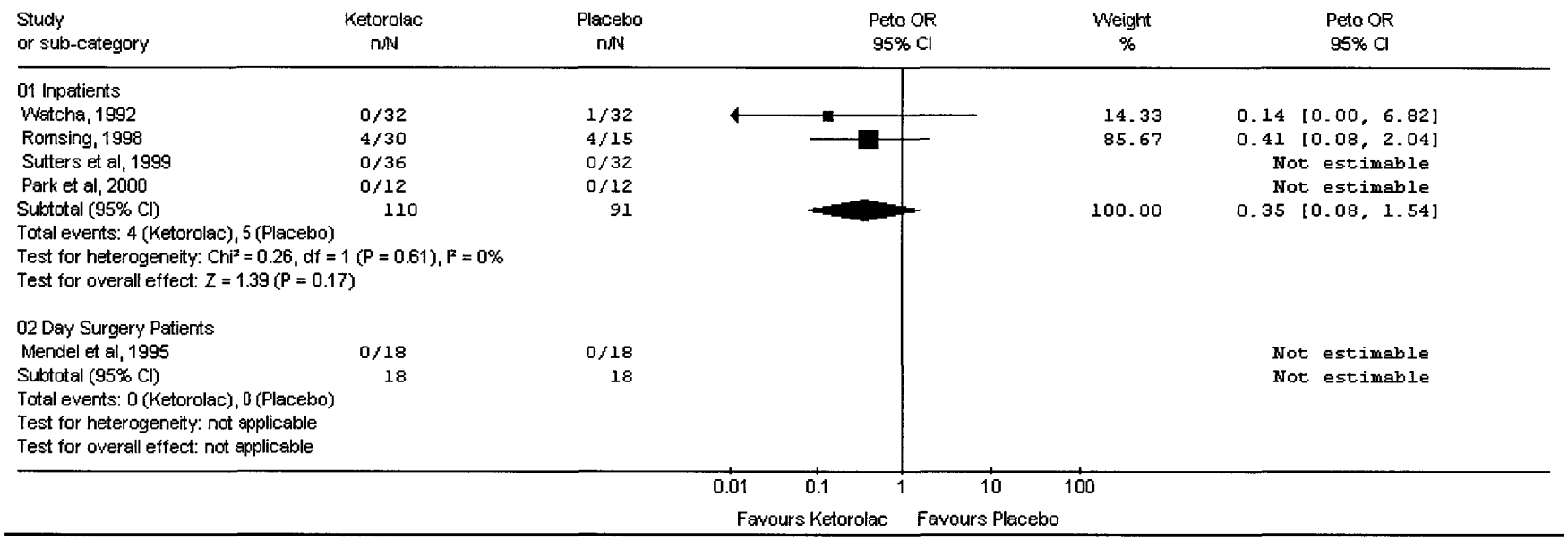

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Figure A-41.

Bleeding – Ketorolac vs. Placebo - High Dose Ketorolac vs. Low Dose Ketorolac

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 11 Bleeding Events - Ketorolac vs Placebo
Outcome: 06 High dose Ketorolac vs Low dose Ketorolac

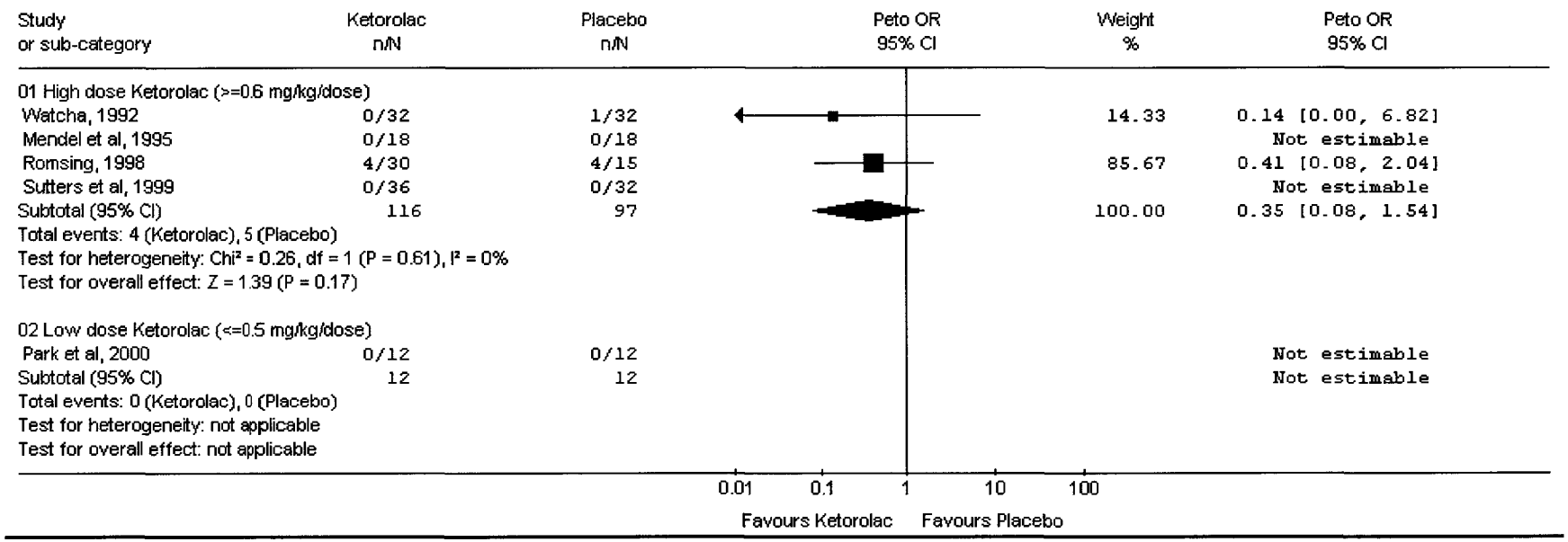

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Figure A-42.

Bleeding – Ketorolac vs. Placebo - Dose Duration >24 Hours vs. Dose Duration <24 Hours

Review: The Role of Intravenous Ketorolac in the Pain Control of Post-Operative Pediatric Patients: A Systematic Review
Comparison: 11 Bleeding Events - Ketorolac vs Placebo
Outcome: 07 >24 hour dosing duration vs <24 hour dosing duration