Intranasal dexmedetomidine for laceration repair in children: a dose finding study

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Dr. Poonai is the lead investigator responsible for trial oversight. Dr. Coriolano is the project coordinator. Dr. Heath is the biostatistician responsible for data analysis. All other investigators

are knowledge experts that will contribute to the design, protocol, results interpretation, and manuscript preparation.

INTRODUCTION

Lay Summary

The most common injury prompting an emergency department (ED) visit in children is a cut (laceration) that requires repair using stitches or skin glue. Despite anesthetic (freezing), laceration repair is often very distressful because in young children, most occur on the face. Distraction techniques are difficult and restraint is often necessary to achieve a cosmetically appealing repair. Although pain can usually be minimized, distress is very difficult to manage in children. Drugs to reduce anxiety in adults such as lorazepam (Ativan^{TM}) often produce greater anxiety in children. There is currently no effective drug to relieve the distress of laceration repair in children. Untreated pain and distress in children results in slower healing, poor appetite and sleep, fear of medical care, and chronic pain. Parents are significantly affected by witnessing their child's discomfort and look to health providers to relieve pain and distress. Our goal is to find a safe and effective drug to reduce distress in children undergoing laceration repair. Dexmedetomidine is a new drug that safely provides mild sedation and can be given as a painless nasal spray. Intranasal dexmedetomidine (IND) has been shown to reduce distress in children undergoing painful procedures such as dental work and intravenous insertion. However, no large study has explored IND for laceration repair. In order for research to change the way we care for children, a large study that enrolls children across many paediatric EDs needs to be performed. The first step is to conduct a smaller study to identify the safest and most effective dose. Our proposed study plans to enroll 55 children age 1-10 years who require laceration repair. Each participant will receive a weight-based dose of IND with 1-2 pairs of nasal sprays. Different doses will be used until the most effective and safe dose is found. All children will receive local anesthetic (freezing) and undergo laceration repair according to standard practice. The two most important outcomes during the procedure are sedation and anxiety. We will record a video of the child during laceration repair and to reduce bias, videos will be scored by research assistants who are not in the ED. The parent, child, nurse, and doctor will rate their satisfaction with the procedure using a 5-point scale. Following discharge, at 24-48 hours, the family will receive a 10-minute Internet-based survey to identify delayed adverse behaviors and at 14 days, a 3-minute survey to record complications related to laceration repair. Our results will be used to design a larger study which may potentially lead to a much less distressing experience for children that require laceration repair. Perceived distress in children is closely tied to caregiver satisfaction and an improved ED experience will lead to a more positive view of the health care team. A more relaxed child will enhance the ability of doctors and trainees to achieve a good cosmetic repair. Given our links with surrounding hospitals where most children with lacerations attend, our results can easily be shared to improve the care of children across Southwestern Ontario and eventually Canada-wide.

Background and Rationale

Lacerations are the most common injury for which children seek care in the emergency department (ED) (1). In Canada, lacerations are one of the top ten presenting complaints in

children under 10 years, comprising nearly 8% of paediatric ED visits (2). Despite the routine application of topical lidocaine-epinephrine-tetracaine (LET) for analgesia, young children routinely resist laceration repair. While distraction may help in older children, in younger children, most lacerations occur on the face (3), making distraction difficult. Untreated pain in childhood can lead to short-term problems such as slower healing and long-term issues such as anxiety, needle phobia, and fear of medical care as adults (4). In 2016, the American Academy of Pediatrics and American Academy of Pediatric Dentistry recommended a goal of minimizing discomfort and pain and controlling behavior and movement during procedures (5). Local or topical anesthetics may reduce pain but do nothing to alleviate procedural distress (6). Many children require light sedation to provide comfort, promote compliance with positioning requirements, and facilitate a timely and cosmetically appealing repair (6)**.** Intranasal midazolam is the most commonly used anxiolytic in children, however, a systematic review found little evidence of benefit (7). Moreover, midazolam has unpredictable efficacy and discomfort with nasal administration is a common complaint (8, 9). Dexmedetomidine is a relatively new alpha-2-adrenergic receptor agonist with anxiolytic, sedative, and analgesic properties (10). Three systematic reviews have suggested intravenous dexmedetomidine is effective for procedural distress in children (10-12). However, intranasal therapies are gaining popularity among health care providers due to ease of administration and less distress. Consequently, our team performed a systematic review of intranasal dexmedetomidine (IND). The review included 18 trials of 2037 children undergoing distressing procedures including intravenous insertion, dental extraction, ophthalmologic examination, and diagnostic imaging (Appendix A). Across trials, IND had an onset and duration of sedation of 7-31 and 41-92 minutes, respectively. IND 1-4 mcg/kg provided adequate sedation in a significantly greater proportion of children (79%, range 55-98%) versus other anxiolytics (midazolam, chloral hydrate) (60%, range 0-96%). There were no serious adverse events and IND was well tolerated in 88% of participants (13). However, heterogeneity in dose and vehicle (mucosal atomizer versus nasal drops) underscored the wide range in effectiveness we observed. Optimizing these factors may produce more consistent and effective sedation. Due to heterogeneity, we were unable to characterize a dose-response relationship and an area of uncertainty is the optimal dose of IND. Only one trial has investigated IND in children for positioning prior to laceration repair. 70% (n=20) of participants were deemed "not anxious" compared to intranasal midazolam (11%, n=18) (3). However, the small sample size and focus on pre-procedural anxiety have limited clinical uptake. A large multicentre trial with an optimized dosing protocol will yield the best estimate of IND's effectiveness. The results will be more likely to improve how the distress of laceration repair is managed. However, this is predicated upon determining recruitment feasibility, protocol compliance, and the most effective dose of IND.

Purpose of the study

Currently, an effective drug to relieve the distress of laceration repair in children is not known. Therefore, purpose of this study is to find a safe and effective drug to reduce distress in children undergoing laceration repair.

Expected Results and Significance

We believe that our study will identify the most efficacious and safe dose of IND, logistic obstacles to recruitment, and a realistic expectation of maximal sedation efficacy. The results will

inform the design of a much larger multicentre randomized trial that will hopefully change practice and improve care.

Objectives

Primary Objective:

In children aged 1 to 10 years who requires a laceration repair using stitches or skin glue, our objective is to determine the most efficacious dose of intranasal dexmedetomidine (IND) in terms of adequate sedation for laceration repair. Adequate sedation for the duration of the laceration repair is measured using the Pediatric Sedation State Scale (PSSS) (14).

Secondary Objectives:

1. To determine how well participants were able to tolerate the IND sprays.
2. To determine the degree of satisfaction with laceration repair on the part of participants and health care providers
3. To determine the feasibility of recruitment
4. To determine the logistic obstacles to implementation

We hypothesize that adequate sedation will be seen at higher doses of IND (3-4 mcg/kg) compared to lower doses (1-2 mcg/kg). Our objectives are to determine: (i) the most efficacious dose of IND in terms of adequate sedation for laceration repair, (ii) tolerability of IND sprays, (iii) patient and provider satisfaction with laceration repair, (iv) feasibility of recruitment, (v) logistic obstacles to implementation

Limitations

Scoring of sedation and anxiolysis are subjective which may lead to an inaccurate determination of the optimal dose. To minimize this risk, the training protocol used in prior studies employing the PSSS will be followed. In addition, a kappa statistic < 0.7 will prompt a re-review of the videos by the PI. Blinding of the different doses will be difficult to accomplish and may be a source of bias. To overcome this, the outcome assessors scoring the videos for sedation (PSSS) and anxiety (YPAS) will be remote from the clinical encounter and the video segment will commence following intranasal drug administration.

Trial Design

This study will be designed as a phase II single-arm dose ranging pilot study using an adapted version of the Continual Reassessment Method (15). CRM is a model-based design that is more likely to determine the correct dose compared to standard 3+3 designs (16). The adapted method adjusts for potential over-sedation (as measured by the PSSS) for higher doses of IND.

METHODS: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

Study Setting

This study will be carried out in the paediatric emergency department (ED) of the Children's Hospital in London, Ontario, Canada.

Eligibility criteria

Inclusion Criteria
We will **include** (i) children age 1-10 years who present to the ED with a single isolated laceration ≤ 5 cm deemed to require single-layer closure using sutures based on the opinion of the treating physician, (ii) predicted to resist positioning for laceration repair based on the opinion of the caregiver, treating physician, child life specialist, or bedside nurse, (iii) lidocaine/epinephrine/tetracaine (LET) used as sole initial topical anesthetic agent

Exclusion Criteria
We will exclude children with (i) laceration repair requiring procedural sedation (without IND) or local nerve block, (ii) other injuries requiring reduction (fracture or dislocation) or repair (nailbed injury or laceration), (iii) lacerations containing foreign body material (including dirt and debris), (iv) history of hypersensitivity to dexmedetomidine, (v) occlusion of at least one nare due to mucus, polyps, septal deviation, etc., (vi) concomitant use of an a2-adrenergic receptor agonist, (vii) bradycardia or hypotension for age (possible transient but clinically insignificant adverse effects of dexmedetomidine), (viii) we will exclude caregivers if they are not the primary care provider, (ix) are unable to read or understand English above at least a grade 8 literacy level, (x) concomitant upper respiratory tract infection or allergic rhinitis with at least one non-patent nare, (xi) known renal insufficiency, (xii) uncorrected mineralocorticoid deficiency, (xiii) congenital heart disease or cardiac conduction disorder

Intervention

Description of intervention

Participants will be consecutively screened for eligibility during the hours of study recruitment (1700 to 2300 hours, 7 days per week) by trained research assistants (RA) prior to being seen by a physician but after nursing assessment. If eligible, the RA will obtain informed consent and assent (when applicable) and the physician will confirm eligibility and order the study intervention on Cerner. Participants will be administered IND 100 mcg/mL [Precedex®, Pfizer Canada Inc, Kirkland, Québec 1-4 mcg/kg (max 200 mcg or 2 mL)]. The weight-based dose will be calculated by REDCap and confirmed by the nurse and physician. The intervention will be drawn into a mucosal atomizer device (MAD) by the bedside nurse using a 1 mL syringe. An extra 0.15 mL will be drawn into the atomizer upon first use to account for dead space. No more than 0.5 mL per nare will be administered at once because volumes exceeding 0.5 mL result in oropharyngeal deposition (17). If two sprays are required (one per nare), they will be administered either simultaneously or in rapid succession. IND will be administered by the bedside nurse with the participant positioned supine with the head at 45^{o}. In our ED, topical anesthetic (LET) is placed on the wound 30 minutes prior to laceration repair once the nurse has obtained a physician's order. IND has a time to peak plasma concentration of 38 minutes (17) and an onset of sedation in children of 25 minutes (18). IND will be given at the same time as LET placement so that the onset of sedation is coincident with positioning for laceration repair. The physician or their designate will be asked to perform suture repair after at least 30 minutes has elapsed following IND administration.

The RA will conduct two follow-ups with participants by email or telephone, depending on the preference of the participant. The RA will contact the participant 24-48 hours post-discharge to identify the presence of delayed maladaptive behaviors using the Post-Hospital Behavior Questionnaire (PHBQ); The PHBQ will take approximately 10 minutes to complete. At 14 days post-laceration repair, participants will be contacted to determine the presence or absence of complications (infection; dehiscence; contracture; retained suture material). This survey will take approximately 3 minutes to complete. If the latter survey cannot be obtained, the medical record of the participant will be examined for the presence of an emergency department visit for wound-related complications.

Criteria for discounting or modifying allocated interventions

An investigator may discontinue or withdraw a participant from the study for the following reasons:

1. If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would be detrimental to the health of the participant.
2. If the participant is found to meet exclusion criteria (either newly developed or not previously recognized) that precludes further study participation.

Concomitant care and interventions that are permitted or prohibited during the trial

Permissible co-interventions include topical and subcutaneous anesthetic, oral or IV analgesics, and non-pharmacologic strategies for pain and distress.

Outcomes

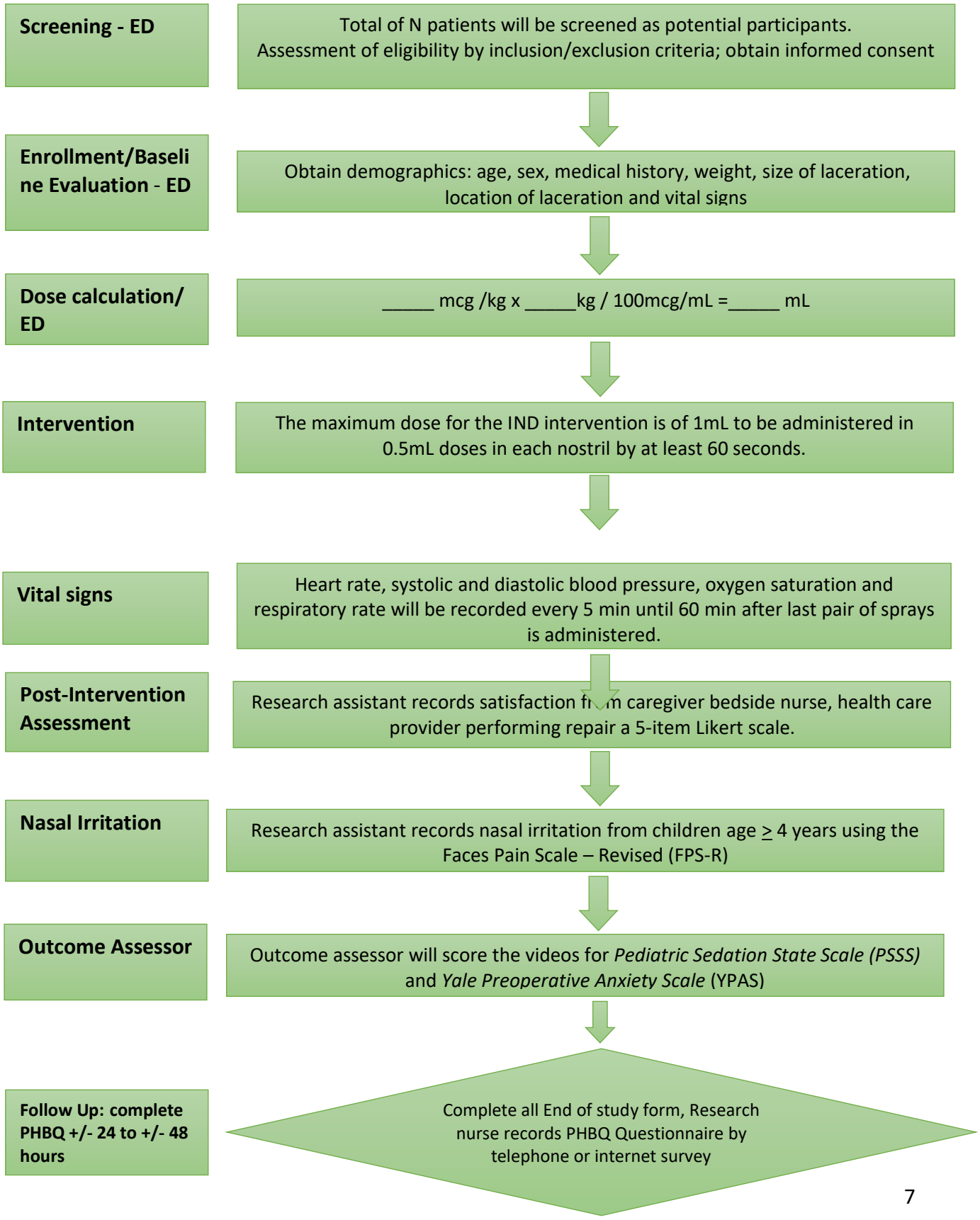
All data will be recorded using Research Electronic Data Capture (REDCap) by RAs. We will collect demographic data: age; sex; size and location of laceration; number of sutures; trainee level (if repair is not performed by attending physician); type of local anesthetic; presence or absence of a child life specialist; distraction techniques; data pertaining to primary and secondary outcomes. The **primary outcome** is adequate sedation (PSSS 2 or 3) for the duration of the measurement period (initial positioning to tying of the last suture). **Secondary outcomes** include: onset and duration of sedation; adverse effects as defined by the Quebec Guidelines (16); anxiolysis during the study period measured using the *Yale Preoperative Anxiety Scale*; compliance (yes/no) with IND administration; satisfaction with laceration repair using a 5-item Likert scale obtained from the caregiver, child (if > 7 years), individual performing the repair, and bedside nurse; nasal irritation from children age > 4 years using the *Faces Pain Scale – Revised* (FPS-R); length of stay; consent rate; heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and oxygen saturation (SpaO2), respiratory rate (RR) recorded at baseline and every 5 minutes until 60 minutes after last pair of sprays is administered, delayed maladaptive behaviors using the *Post-Hospital Behavior Questionnaire* (PHBQ) assessed 24-48 hours post

discharge; complications within 14 days of discharge (infection; dehiscence; contracture; retained suture material).

Patient Engagement

Study outcomes were identified and agreed upon by a five-member focus group involving the PI, a child life specialist, and three parents of children who have undergone laceration repair. The study design therefore reflects their concerns about length of stay and topical analgesia.

Participant timeline



Sample Size
This was calculated using the *Bayesian Continual Reassessment Method* (18). Based on an adverse event rate of 20%, an "effect size" of 1.6 (i.e. the odds ratio between consecutive increasing doses), and a phase II trial accuracy level of 60%, we estimated a sample size of 50 participants. With increasing the sample size by 10% to account for dropouts, the final sample size is 55 participants.

Feasibility
An existing team of 12 research assistants (RAs) with REDCap and clinical trial recruitment experience are available to recruit during the peak visit period of 1700-2300 hours, 7 days a week, 50 weeks a year. A 2018 clinical informatics search revealed that 1332 laceration repairs were performed, of which 472 met our inclusion criteria and presented between 1700-2300 hours. With an expected 50% consent rate, recruitment of 50 participants is feasible in 12 months.

Recruitment

METHODS: ASSIGNMENT OF INTERVENTIONS

Allocation

Not applicable

Sequence generation

A list will be provided to

Allocation concealment mechanism

Not applicable

Implementation

Participants will be assigned to each dosing level by pharmacy based on the continual reassessment method's study design. Research assistants will enroll participants.

Blinding

Blinding of dose levels will not be possible for clinical and research personnel in the ED. However, outcome assessors will be blinded by virtue of being remote from the clinical encounter. Furthermore, video segments will commence immediately after intranasal sprays are given so outcome assessors will not see what volume is administered. Two independent assessors will score each video and an inter-rater agreement (kappa) will be calculated. Disagreements on

scoring for the purposes of estimating the Bayesian dose response model will be resolved by discussion.

METHODS: DATA COLLECTION, MANAGEMENT, AND ANALYSIS

Data collection methods

Sedation will be measured using the Pediatric Sedation State Scale (PSSS) (Appendix B), an instrument validated for video scoring of children undergoing painful procedures. The PSSS is scored from 0 to 5 easily by non-medical personnel. The PSSS assesses pain as well as over sedation and under sedation. *Adequate sedation* is a score of 2 or 3, over sedation is a score of 0 or 1 and under sedation is a score of 4 or 5 (14). Participants will be assigned to doses of IND from 1-4 mcg/kg, increasing in whole number increments. Initially three participants will receive 1mcg/kg and the number of participants at each dose of IND will be recorded. Data from these participants will be used to update a Bayesian model for the dose-response curve for all three categories of sedation. The following three participants will be assigned the dose with the highest posterior probability of an efficacy close to 0.8. This balances the need to determine the most efficacious dose but prevents an excessive number of over-sedations. For the Bayesian dose response model, a determination will be made as to the overall score category for each participant ("adequate", "over", or "under sedated" based on the PSSS). To be scored as "adequate", a participant must have a PSSS score of 2 or 3 for at least 90% of observations from initial positioning to tying of the last suture. If a participant does not retain a PSSS score of 2 or 3 for at least 90% of the observations, they will be categorized as either over or under-sedated, if the majority of the remaining PSSS scores are 0 or 1 or 4 or 5, respectively. Furthermore, if the participant remains awake, but not distressed during the procedure, they will be scored as a 2 based on the PSSS. However, for the purposes of the Bayesian dose response model, they will be scored as "under sedated" to avoid concluding that a lower dose of IND is effective based on the outcomes for participants that did not require sedation. Finally, participants who are noncompliant with IND will be categorized as an over-sedation as it is assumed that this dose was not well tolerated by the participant and dose escalation should be avoided.

Preliminary results indicate that, conditional on suitable priors, this method has an approximately 83% chance of selecting the most effective dose. Serious adverse events as defined by the Quebec Guidelines on paediatric procedural sedation (19) will be reported as per Good Clinical Practices. Data will be reviewed after each dose by a data safety monitoring board (DSMB), who will confirm it is safe to escalate to the dose proposed using the Bayesian dose response model. The DSMB will be comprised of two emergency physicians and will be independent from the sponsor and reporting structure. Permissible co-interventions include topical and subcutaneous anesthetic, oral or IV analgesics, and non-pharmacologic strategies for pain and distress.

Data management

The site investigator will be responsible for retaining (archiving) their own essential study documents that individually or collectively permit the evaluation and conduct of the study and the

quality of data, in accordance with ICH-GCP and applicable regulatory requirements. All study documents, including source, are to be stored in a confidential location with secured and limited access. All electronic records and data sets will be encrypted and password protected with access only permitted by the PI, site coordinator(s), and research team members. Paper data (e.g. copies of consent and assent forms) will be stored exclusively in the Participating Site Investigator's research office in a locked cabinet. Results will not be reported in a way that identifies any individuals.

All study related documentation will be retained in accordance with Health Canada's Food and Drug Regulations for 25 years and per the investigational site's institutional record management and retention policies. No records will be destroyed without the written consent of the Qualified Investigator and/or Sponsor.

Statistical methods

For demographic data and all secondary outcomes, we will summarize the data using
i) proportions for discrete variables
ii) means, medians, standard deviation, interquartile range and range for continuous variables
For the primary outcome, we will also provide the Bayesian credible interval for the probability of a successful sedation, estimated from the Bayesian dose response curve. We will provide a graphical summary of patient flow and the dose escalation process. No imputation is planned for missing data and, unless unexpectedly high levels of missingness are observed, data will be assumed to be missing at random and missing data points will be excluded from the analysis. Available data for the primary outcome will be a requirement for all 3 patients at each dosing level before proceeding with the next dose. In keeping with methodologic guidelines for dose-finding studies, inferential analyses will not be performed and will focus instead on a non-frequentist confidence interval estimation approach.

Data monitoring

Data will be reviewed after each dose by a data safety monitoring board (DSMB), who will confirm it is safe to escalate to the dose proposed using the Bayesian dose response model. The DSMB will be comprised of two emergency physicians and will be independent from the sponsor and reporting structure.

METHODS: MONITORING

Harms

Study Assessment and Procedures Assessment of Safety

The onset of sedation, duration of sedation, maladaptive behaviors due to sedation, nasal irritation, vital signs are also important measures used to assess safety.

Onset of sedation*:* This will be defined as the time interval from administration of the first pair of IN sprays to the time when a PSSS score of 2 or 3 is achieved, whether or not all of the intervention has been administered. This will be ascertained by the outcome assessors.

Duration of sedation: This will be defined as the duration of time between the first PSSS score of 2 or 3 to the last PSSS score of 2 or 3 post- laceration repair. This will be ascertained by the outcome assessors.

Maladaptive behaviors due to sedation: This will be assessed by the research associate using the Post-Hospital Behavior Questionnaire (PBHQ) administered by phone or email survey 24 to 48 hours following discharge. This will be done in order to screen for any delayed behavioral adverse effects. This information will be recorded using REDCap (Dose Finding Study PHBQ form).

Nasal irritation: The research assistant will ask participants age $\geq$ 4 years using the Faces Pain Scale – Revised (FPS-R) to rate their nasal irritation related to the IN sprays. Nasal irritation has not been described with IN dexmedetomidine but is theoretically possible and needs to be identified in order to provide appropriate anticipatory guidance.

Vital Signs: Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and oxygen saturation (SpaO2), respiratory rate (RR) will be recorded at baseline and every 5 minutes until 60 minutes after last pair of sprays is administered. Data will be collected using REDCap (Vital signs CRF form).

Adverse events (AEs): The research associate will be trained on the recognition and definition of all expected and unexpected AEs. AEs are document medical events that occur to a participant/subject once enrolled in a study. AEs are the construct through which the safety of an intervention is recorded and assessed during the study period.

Data will be collected using REDCap (Dose finding Study AE form). The form includes the definitions and AE descriptions that could be related to sedation. Uncertainty regarding the presence of AEs will be clarified with the sedating physician (if it occurs while participant is in the paediatric emergency department) and with PI for all AE cases reported. All AEs will be recorded.

Monitoring of Adverse Events During Sedation

In two systematic reviews (11, 13) of intranasal dexmedetomidine in children (29 trials, 3134 participants), adverse cardiorespiratory events requiring intervention have not been described. This is in contrast to the use of IV dexmedetomidine and may be explained by the reduced bioavailability of the intranasal route (median 65%). However, to monitor the presence of serious adverse effects, several measures will be in place. Commencing immediately prior to administration of the intervention and continuing until the participant is awake, all participants will receive continuous cardiorespiratory monitoring. In accordance with our institutional policies

and recommendations from the American College of Emergency Physicians' Guidelines, this consists of:

1. Five-lead continuous ECG to assess for the presence of bradycardia, dysrhythmias, and early changes suggestive of hypokalemia (< 3 mEq/L) (flattened or inverted T waves progressing to QT prolongation, ST depression, and U waves). If suggestive ECG changes are present, the participant will have a stat capillary puncture to measure the serum potassium.
2. Oxygen saturation to assess for the presence of desaturation
3. Blood pressure assessments using a Dynamap every 5 minutes to assess for the presence of hypotension or hypertension

A staff anesthetist is in house 24-7 in our institution. In the event that an adverse electrolyte or cardiopulmonary event is identified, the appropriate resuscitative measures will be provided based on the opinion and direction of the treating paediatric emergency physician. In our institution, resuscitative measures in the emergency department fall under the responsibility of the treating paediatric emergency physician. In the event of clinically significant hypokalemia, this may include but is not restricted to oral potassium chloride. In the event of clinically significant hypotension or bradycardia, this may include but is not restricted to reverse Trendelenberg positioning, placement of an intravenous line and administration of crystalloid fluids, and other measures consistent with the Paediatric Advanced Life Support algorithm.

Serious Adverse Event and Unexpected Drug Reactions

A **Serious Adverse Event (SAE)** will be defined as - any adverse occurrence of a clinical trial subject who is administered a drug at any dose, or placebo that may or may not be caused by the administration of the drug or placebo that results in:

1. Hospitalization due to a sedation related event
2. Prolongation of existing hospitalization
3. Congenital malformation or birth defect
4. Persistent or significant disability or incapacity
5. An outcome that is life-threatening
6. Death

Important medical events that may not result in death, be life-threatening, substantially disrupt one's ability to conduct normal life functions or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

All serious, unexpected AEs and drug reactions will be reported to Health Canada by the Qualified Principal Investigator within 15 calendar days after the Qualified Principal Investigator becomes aware of the event. For death or life-threatening events, this report must be done within 7 calendar days after the Qualified Principal Investigator becomes aware of the event. In the latter

case, a follow-up report must be filed within 8 calendar days. All AEs will also be submitted, in accordance with the DSMB safety monitoring plan to the independent DSMB assigned to this study.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the PI deems the event to be chronic or the participant is stable. The Qualified Principal Investigator will also, within 8 days after having informed Health Canada of the adverse drug reaction, submit as complete as possible, a report which includes an assessment of the importance and implication of any findings.

A completed Adverse Drug Reaction (ADR) Expedited Reporting Summary Form should be attached to the front of the completed ADR report (suggested ADR report format: Suspect Adverse Reaction Report - CIOMS form of the Council for International Organizations of Medical Sciences (CIOMS)). Please find the form attached as Appendix C.

Adverse Events Reporting

All adverse events (AEs) will be reported to the Research Ethics Board in accordance with site's AE reporting guidelines. The PI will assess each AE in terms of its expectedness and relationship to the study drug. Information to be collected will include an event description, date of onset, clinician's assessment of severity, relationship to study intervention (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event and event outcome (resolved/recovered, recovered with sequalae, not recovered/not resolved, death, or unknown).

Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause based on the findings of the DSMB of safety issues. The latter include determination by the DSMB of significant adverse events that pose an unacceptable risk to participants such as complications due to treatment or related adverse events at rates above expected. Serious adverse events as defined by the Quebec Guidelines (16) on paediatric procedural sedation will be reported as per Good Clinical Practices. Data will be reviewed by the two-member DSMB prior to each planned dose increase. The two members will need to unanimously agree that it is safe to increase the dose. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party (DSMB) to study participants, funding agency (if applicable), the Sponsor, responsible REB and Health Canada. The Study participants will be contacted by Qualified Principal Investigator, as applicable, and be informed of changes to study visit schedule (if applicable). The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, REB and/or Health Canada.

Withdrawal / Discontinuation Criteria

Participants are free to withdraw from participation in the study at any time upon request. However, data accrued from the participant to the time of withdrawal will be retained by the investigators for analysis. Example, if participant decided to withdraw the study before receiving the intranasal sprays. All data up to the point participant requested to be withdrawn will be kept. An investigator may discontinue or withdraw a participant from the study for the following reasons:

1. If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would be detrimental to the health of the participant.
2. If the participant is found to meet exclusion criteria (either newly developed or not previously recognized) that precludes further study participation.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Dose Finding Study Case Report Form (CRF- End of Study Form). For the purposes of this trial, a protocol violation will be defined as *any accidental or unintentional change or non-compliance with the REB approved protocol which increases or decreases benefit, affects the subject's rights, safety or welfare or the integrity of the study*. In the event that a participant is found to meet exclusion criteria (either newly developed or not previously recognized), this constitutes a protocol violation and the protocol will be discontinued. However, the participant will be followed for the study period for AEs. A protocol violation report must be completed as per local REB requirements and notification should be sent to the local REB (Western University - Research ethics board) by email. A note to file signed by the site PI should be completed and if any clinical adverse event (AE) occurs, an AE should also be completed and signed by PI and research staff. A copy of all documents must be sent to the local REB.

Follow up for participants withdrawn from investigational product: All participants who receive the interventional drug, including those who withdrawn, will be asked to remain in the emergency department until they are fully recovered from sedation as per the treating physician. Participants who are withdrawn after receiving interventional product will be contacted approximately 24 to 48 hours after discharge by a research associate via telephone. These participants will be asked an open-ended question such as: <u>do you have any health concern since you were discharged from paediatric emergency department?</u> If they return to the emergency department within 24 hours, the participant's medical record will be scrutinized by the research associate for adverse events as defined by the Quebec Guidelines (16) on paediatric procedural sedation.

Caregivers and participants will be advised at discharge and during the follow-up phone call that if they (or their child as applicable) experience adverse effects that they believe require a hospital visit, it is important that they make every effort to return to the hospital where procedure was performed. If they need immediate treatment and are unable to return to the hospital, they should proceed to the nearest emergency as soon as possible

Quality Assurance and Quality Control

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

The investigational site will provide direct access to all trial-related source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

All individuals from the research team such as site Investigator, site coordinators, and other research personnel will be required to complete the Tri-Council Policy Tutorial: Ethical Conduct for Research Involving Humans, the Good Clinical Practices course, and the division 5 Health Canada module. Completion will be documented prior to implementation of the study. Privacy and confidentiality policy and procedure will also be reviewed at the study recruitment training session for all study personnel.

Auditing

The investigational site will provide direct access to all trial-related source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

ETHICS AND DISSEMINATION

Statement of Compliance

The trial will be conducted in accordance with Good Clinical Practice (GCP) as described in Health Canada's section C.05.010/Division 5 of the Food and Drugs Regulations, International Conference on Harmonization-Good Clinical Practice (ICH-GCP E6 R2), Tri-Counsel Policy Statement (TCPS2, 2014); applicable federal, provincial and local regulatory and legislative requirements. The Qualified and Participating Site Investigator(s) will assure that no deviation from, or changes to the protocol will take place without prior documented authorization (no objection letter - NOL) from Health Canada (Therapeutic Products Directorate) and documented approval from a duly constituted Research Ethics Board (REB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH-GCP Training.

Research ethics approval

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the REB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled.

Protocol amendments

Any amendment to the protocol will require review and approval by the REB before the changes are implemented to the study as well as authorization form Health Canada. All changes to the consent form will be REB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form

Consent or assent

If a patient is eligible, the Research Assistant will obtain informed consent and assent (when applicable).

Confidentiality

Please refer to the data management section. All identifying participant information will be kept confidential in accordance with our REB requirements. The REDCap project will contain no identifying information.

Declaration of interests

None

Access to data

All electronic records and data sets will be encrypted and password protected with access only permitted by the PI, site coordinator(s), and research team members. The investigational site will provide direct access to all trial-related source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities

Ancillary and post-trial care

Post-sedation care and monitoring will be in accordance with local institutional policies for sedated patients. Discharge instructions appropriate to laceration repair will be provided.

Dissemination policy

Trial results in the form of an abstract will be presented at local research days and national scientific meetings. The manuscript will be submitted to a peer reviewed medical journal. Results will be disseminated informally to the study team and health care personnel at the participating site. There are no plans for dissemination of results directly to participants.

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APPENDICES

Appendix A

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

PEDIATRICS

Intranasal dexmedetomidine for procedural distress in children: a systematic review

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Keyword/Topic:	Anesthesiology/Pain Medicine

Title

Intranasal dexmedetomidine for procedural distress in children: a systematic review

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Abbreviations:

ABR auditory brainstem response
CI confidence interval

CT computed tomography
FLACC Faces Legs Activity Cry Consolability
GRADE Grading of Recommendations Assessment, Development, and Evaluation
IN intranasal
IND intranasal dexmedetomidine
IQR interquartile range
MAD mucosal atomizer device
IV intravenous
MRI magnetic resonance imaging
OR odds ratio
TTE transthoracic echocardiography
VEPs visually evoked potentials

Table of Contents Summary: This systematic review of 19 trials (2137 participants) summarized the effectiveness of intranasal dexmedetomidine for procedural distress in children.

What's Known on This Subject: Painful and distressing procedures are commonly performed in children. Oral and intranasal midazolam, the most commonly used anxiolytics have limited evidence of benefit. Intranasal dexmedetomidine is a relatively new agent but its study has been limited by small sample sizes.

What This Study Adds: Intranasal dexmedetomidine may provide more effective sedation than chloral hydrate or midazolam. Limited data exist for minor, painful procedures such as laceration repair or lumbar puncture. The benefits of administration must be weighed against the potential for adverse cardiovascular effects.

Contributor's Statement

Drs. Poonai, Ali, Hartling and Mr. Spohn conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.
Mr. Hendrikx conducted the literature search, and reviewed and revised the manuscript.
Mr. Spohn designed the data collection instruments and collected data and reviewed and revised the manuscript.
Mr. Vandermeer carried out the initial analyses and reviewed and revised the manuscript.
Drs. Joubert, D.Trottier, Shah, Sabhaney, and Bhatt critically reviewed the manuscript for important intellectual content.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

ABSTRACT

Context: Intranasal dexmedetomidine (IND) is an emerging agent for procedural distress in children.

Objective: To explore the effectiveness of IND for procedural distress in children.

Data Sources: We performed electronic searches of MEDLINE (1946-2019), EMBASE (1980-2019), Google Scholar (2019), CINAHL (1981-2019), and Cochrane Central Register.

Study Selection: We included randomized trials of IND for procedures in children.

Data Extraction: Data extraction was performed in duplicate. Methodological quality and quality of evidence were evaluated using the *Cochrane Collaboration's Risk of Bias* tool and the *Grading of Recommendations Assessment, Development, and Evaluation* system, respectively. The primary outcome was the proportion of participants with adequate sedation.

Results: Among 19 trials (n=2137), IND was superior to oral chloral hydrate (3 trials), oral midazolam (one trial), intranasal midazolam (one trial), and oral dexmedetomidine (one trial). IND was equivalent to oral chloral hydrate (two trials), intranasal midazolam (two trials), and intranasal ketamine (three trials). IND was inferior to oral ketamine and a combination IND plus oral ketamine (one trial). Higher doses of IND were superior to lower doses (four trials). Adverse effects were reported in 67/727 (9.2%) participants in the IND versus 98/591 (16.6%) in the comparator group. There were no reports of adverse events requiring resuscitative measures.

Limitations: Adequacy of sedation was subjective; possibly leading to biased outcome reporting.

Conclusions: Given the methodological limitations of included trials, IND is likely more effective at sedating children compared to oral chloral hydrate and oral midazolam. However, this must be weighed against the potential for adverse cardiovascular effects.

INTRODUCTION

In hospital, painful and distressing procedures including laceration repair, lumbar puncture (1), intravenous (IV) insertion (2-6), and venipuncture (6, 7) are common. However, administration of analgesia is inconsistent for painful procedures and procedural distress is poorly managed (2-6). A Canadian survey of over 3000 hospitalized children found that they received more than six painful procedures per day, and less than one third of them received analgesia (8). Such procedures result not only in the reported pain, but also in closely-linked procedural distress, which often requires a different approach than simply analgesia. Further, other non-painful diagnostic procedures, such as CT and magnetic resonance imaging (MRI), require a child to lie motionless which can be anxiety-provoking across the age spectrum, and often requires some level of sedation for younger patients.

To address these issues of sedation and anxiolysis, intranasal (IN) therapies for procedural distress can be non-invasively administered (9) and require less procedural skill than IV insertion (10). Currently, midazolam is the most commonly used anxiolytic in children because of its rapid onset of action and amnestic properties (11). However, when used via the IN route, it has an unpleasant taste, can be irritating to the nasal mucosa (12, 13), and has adverse effects (11, 14), underscoring the need for appropriate monitoring. Furthermore, two Cochrane reviews have differing conclusions regarding midazolam's effectiveness for children's procedures (11, 14), suggesting that additional evidence for alternative agents is needed.

Dexmedetomidine is a central α_2-adrenergic receptor agonist with analgesic and anxiolytic properties and its use outside the intensive care and pre-anesthetic setting is gaining popularity (15). Three systematic reviews suggest dexmedetomidine, is effective for procedural

distress in children (15-17). However, they mainly reported effects by IV route and only one explored intranasal dexmedetomidine (IND), focusing on anesthetic premedication (16). To date, no large trial or review exists to guide the use of IND for procedural distress in children. With the emerging popularity of dexmedetomidine for procedural distress and a desire for less invasive approaches in children, a comprehensive review of IND is needed to guide its use. We sought to summarize the effectiveness of IND for children undergoing painful and distressing procedures.

PATIENTS AND METHODS

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (18) (Appendix 1).

Eligibility Criteria

We included all published and unpublished randomized trials comparing IND as monotherapy to any comparator for a procedure in children under 19 years and reported adequacy of sedation. Trials of both adults and children were included if the authors provided pediatric-specific data. We excluded sub-studies, crossover studies, abstracts with insufficient information, and studies of anesthetic premedication unless they involved a painful procedure.

The primary outcome was the proportion of participants deemed to be adequately sedated based on the investigators' opinion. Clinically, we believed this to be the most pragmatic, relevant, and feasible approach to describing relief of procedural distress. Methodologically, we believed this to be consistent way of overcoming differences in sedation scales. Secondary outcomes included need for additional sedation, onset and duration of sedation, length of stay, analgesia, adverse events, and acceptance of IN administration.

Data Sources

A medical librarian (SH) developed the search strategy. We performed electronic searches of MEDLINE (1946 – 2018), EMBASE (1980 –2018), Scopus (2018), Web of Science (2018), Google Scholar (2018), Cochrane Central Register (2018), and CINAHL (1981 to 2018). The search was completed in January 2018 and repeated in February and July 2019 without language restriction (Appendix 2). Our gray literature search was informed by the Canadian Agency for Drugs and Technologies in Health checklist (19). We checked reference lists of included trials and systematic reviews. We contacted corresponding authors when data on the primary outcome was missing.

Study Selection and Data Extraction

Two authors (NP, JS) independently screened titles, abstracts, and full-texts for inclusion. Disagreements were resolved through discussion. The primary author entered the data into Review Manager version 5.2.11 and GRADEpro version 3.6.

Risk of Bias in Individual Studies

Two authors (NP, JS) independently evaluated methodological rigor using the Cochrane Collaboration's Risk of Bias tool (20) and outcome-specific ratings of the overall quality of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (21).

Summary Measures and Synthesis of Results

A priori we considered meta-analyses if there was homogeneity in procedures, dosing regimen, and outcome measures. However, meta-analyses were not performed on any outcome due to substantial heterogeneity. Instead, we conducted a descriptive analysis of each study's design, population, and primary outcome. Based on the classification system of Tricco et al. (22), we categorized the results of individual studies based on the outcome of adequate sedation as:

unfavorable (effect in favor of the comparator with p value ≤ 0.05); *neutral* (non-statistically significant difference between interventions with p value > 0.05)); *favorable* (effect in favor of the experimental agent, IND, with p value ≤ 0.05); *indeterminate* (unable to judge due to conflicting and multiple primary outcomes). We used ranges to describe onset and duration of sedation and length of stay. We used proportions to describe acceptance of IN administration. Agreement between reviewers was described using raw agreement.

Risk of Bias Across Studies

Publication bias was assessed using a funnel plot.

Additional Analyses

We evaluated statistical heterogeneity using the I^2 statistic.

RESULTS

Study Selection

Nineteen trials (n=2137) were included. Thirteen involved IND versus a non-IND comparator. Six compared different doses of IND or methods of IND administration (Figure 1).

Study Characteristics

IND was studied for the following non-painful procedures: ophthalmic examination (3 trials) (23-25); transthoracic echocardiography (TTE) (2 trials) (26, 27); auditory brainstem response (ABR) testing (2 trials) (28, 29); computed tomography (CT) (3 trials) (29-31), magnetic resonance imaging (MRI) (2 trials) (32, 33); visually evoked potentials (VEPs) (1 trial) (29) and was studied for the following painful procedures: IV insertion (6 trials) (31, 34-38), laceration repair (1 trials) (39), and dental work (2 trials) (40, 41). All trials were published in English in peer reviewed journals and included 2137 children (847/2093, 40.5% females), age 1 month to 14 years. Demographic statistics excluded Patel et al. (41) because these details were

not specified. IND was compared to oral dexmedetomidine (41), chloral hydrate (23, 26, 28, 30, 33), IND plus oral ketamine (37), IN or oral midazolam (31, 34, 39, 40), IN or oral ketamine (35-37, 40). Six trials compared different doses of IND (24, 25, 29, 32) or methods of IND administration (27, 38) (Table 1).

Risk of Bias Within Studies

Most trials were judged as *low* risk of bias for random sequence generation, blinding, incomplete outcome data, and selective reporting (Figure 2). For allocation concealment, most trials were judged as *unclear* risk of bias. Li et al. was judged as *high* risk of bias for incomplete outcome data because 14/67 participants receiving IND 1 mcg/kg withdrew post-randomization with no outcome data reported (29). Surendar et al. reported vital signs instead of adverse effects and was judged as *unclear* risk of bias (40).

Risk of Bias Across Studies

The overall quality of evidence based on the GRADE system was judged as *high* (length of stay), *moderate* (need for additional sedation, duration of sedation, and adverse effects), or *low* (adequacy of sedation, onset of sedation, and analgesia) (Figure 3).

Adequacy of Sedation

Adequacy of sedation was reported in 18 of 19 trials. A validated sedation instrument was used in ten trials (25-27, 29-34, 36) and included the Observer's Assessment of Alertness/Sedation, Modified Observer's Assessment of Alertness/Sedation Scale, Ramsay Sedation Scale, and the University of Michigan Sedation Scale (Table 1). Seven trials used non-validated scales to measure sedation (24, 28, 35-37, 40, 41). Two trials did not report adequacy of sedation but pain during IV insertion using the Faces Legs Activity Cry Consolability (FLACC) scale (38) and anxiety during early stages of laceration repair using the Yale

Preoperative Anxiety Scale (YPAS) (39). The proportion of participants with adequate sedation was 33/41 (80.4%) for IND plus oral ketamine, 1086/1362 (79.7%) for IND, 241/318 (75.7%) for chloral hydrate, 28/41 (68.3%) for oral ketamine, 59/102 (57.8%) for intranasal ketamine, 30/69 (43.4%) for intranasal midazolam, 7/29 (24.1%) for oral midazolam, and 0/22 (0%) for oral dexmedetomidine. IND was deemed "favorable" versus chloral hydrate in three trials (23, 28, 33), oral midazolam in one trial (31), intranasal midazolam in one trial (34), and oral dexmedetomidine in one trial (41). IND was deemed "neutral" versus chloral hydrate in two trials (26, 30), intranasal midazolam in two trials (39, 40), and intranasal ketamine in three trials (35, 36, 40). IND was deemed "unfavorable" versus oral ketamine and a combination IND plus oral ketamine in one trial (37).

Adequacy of Sedation for Painful and Non-Painful Procedures

For painful procedures (31, 34-41), IND provided adequate sedation to 145/237 (61.2%) versus 151/321 (47.1%) participants among comparators. For non-painful procedures (23-33), IND provided adequate sedation to 862/1025 (84.1%) versus 250/347 (72.0%) participants among comparators. Limiting the comparison of painful versus non-painful procedures to trials using validated instruments, IND versus comparators provided adequate sedation to 24/30 (80%) versus 16/30 (53.3%) participants (painful), and 874/1021 (85.6%) versus 214/277 (77.3%) participants (non-painful), respectively.

Differing Doses of IND and Routes of Nasal Administration

Six trials compared different doses or routes of IND administration. Gan et al. found that 2 mcg/kg provided adequate sedation to significantly more participants undergoing ophthalmologic examination than 1 mcg/kg (28/30, 93% versus 20/30, 67%, respectively; p=0.02) (24). Chen et al. found that 2 and 3 mcg/kg provided a similar degree of sedation for

287 ophthalmologic examination; successfully sedating 49/50 (98%) and 50/50 (100%) participants,
288 respectively (25). Tug et al. found IND 4 mcg/kg provided adequate sedation to significantly
289 more participants undergoing MRI than 3 mcg/kg (20/30, 66.7% versus 7/30, 23.3%,
290 respectively; p=0.003) (32). Li et al. found that higher doses of IND (1 versus 1.5 versus 2
291 mcg/kg) provided adequate sedation to increasingly more participants undergoing CT scan, ABR
292 testing, or VEPs [56/67 (83.6%), 66/74 (89.2%), and 51/53 (96.2%), respectively; p=0.03] (29).
293 Li et al. found no differences in adequate sedation for IND 3 mcg/kg by mucosal atomizer device
294 (MAD) or nasal drops [113/137 (82.5%) versus 120/142 (84.5%), respectively; p=0.57] (27). Xie
295 et al. found that the median (IQR) FLACC scores were significantly better with IND 2 mcg/kg
296 via an MAD versus nasal drops for IV insertion [1 (0.4) versus 3 (4); p=0.02, respectively] (38).
297 **Need for Additional Sedation**
298 Five trials reported on the need for additional sedation (26, 28, 31, 36, 39). Additional
299 sedation was provided to significantly fewer participants in the IND (22/223, 9.9%) versus
300 comparator groups (47/167, 28.1%).
301 **Onset of Sedation**
302 Onset of sedation was reported in 11 trials (23, 25, 26, 28, 30, 33, 34, 36, 37, 40, 41) and
303 ranged from 7-31 minutes for IND and 7-44.2 minutes for comparators. Onset of sedation varied
304 by dose of IND: 1 mcg/kg (14.3-19 minutes) (24, 29, 33, 34, 40), 1.5 mcg/kg (18.1-20 minutes)
305 (29, 40), 2 mcg/kg (8.8-25 minutes)(23-26, 29, 33, 38, 41), 2.5 mcg/kg (7-20.6 minutes) (37, 41),
306 3 mcg/kg (13-31 minutes) (25-28, 30, 32, 36), and 4 mcg/kg (30 minutes) (32).
307 **Duration of Sedation**
308 Duration of sedation was reported insix trials (23, 25, 26, 33, 36, 40) and ranged from 41-
309 91.5 minutes for IND and 77-85.9 minutes for comparators.

310 **Length of Stay**

311 Length of stay was reported in four trials (23, 24, 26, 39) and ranged from 76.8-156
312 minutes for IND and 95-144 minutes for comparators.

313 **Analgesia**

314 Analgesia was reported using the FLACC scale by Surendar et al. (40) in children
315 undergoing dental procedures and Xie et al. (38) in children undergoing IV insertion. The
316 FLACC scale is scored from 0 to 10, with higher scores denoting greater pain (42). Using a
317 pairwise comparison, Surendar et al. reported mean (SD) FLACC scores for IND 1 mcg/kg [3.8
318 (0.8)], 1.5 mcg/kg [3.7 (0.9)], and IN ketamine 5 mg/kg [3.5 (0.7)] were significantly lower than
319 IN midazolam 0.2 mg/kg [5.6 (1.1)] (p value not reported) (40). Xie et al. reported a lower
320 median (IQR) FLACC score for IND 2 mcg/kg by MAD [1 (3.5)] versus nasal drops [3 (4)]
321 (p=0.02) (38).

322 **Adverse Events**

323 Adverse events were reported in all trials except Surendar et al. (40). Across the
324 remaining 18 trials, the most common adverse events of IND, IND plus another sedative, or non-
325 IND comparator were bradycardia [32/1484 (2.2%), 0/41 (0%), and 6/595 (1%), respectively],
326 hypotension [18/1484 (1.2%), 0/41(0%), and 9/595 (1.5%), respectively], oxygen desaturation
327 [7/1484 (0.5%), 0/41 (0%), and 12/595 (2%), respectively], and vomiting [6/1484 (0.4%), 3/41
328 (7.3%), and 47/595 (7.9%), respectively]. No trials used objective criteria to define adverse
329 events. No trials reported the occurrence of upper airway obstruction, apnea, death, the delivery
330 of positive pressure ventilation, chest compressions, vasoactive medications, endotracheal
331 intubation, or neuromuscular blockade.

332 **Acceptance of IN Administration**

Four trials reported acceptability of IN administration. Zhang et al. reported all 94 participants tolerated IND "without crying" (33). Xie et al. reported 25/49 (51%) versus 22/57 (38.6%) participants "calmly accepted" IND using an MAD versus drops, respectively (38). Patel et al. reported acceptance of IND was "fair to excellent" in 16/22 (72.7%) of participants. Surendar et al. reported IND and IN midazolam were "well accepted" by all 84 participants (40).

Agreement Between Reviewers

Two independent reviewers (NP, JS) agreed 102/114 (89.5%) times on risk of bias assessments, 366/430 (85.1%) times on abstract screening and 74/79 (93.7%) times on full-text screening.

Publication Bias

The funnel plot for adequacy of sedation showed some asymmetry (Appendix 3).

DISCUSSION

In this review, the overall quality of evidence for adequacy of sedation was "low". Although our findings suggest that IND likely provides adequate sedation to a greater proportion of children than conventional sedatives (oral midazolam and chloral hydrate), trial results could not be pooled and larger and more methodologically rigorous trials are needed prior to widespread implementation. Clinicians considering the use of IND to alleviate procedural anxiety in children must weigh the benefit of superior sedation against the potential for adverse cardiovascular effects, which require further rigorous study to fully assess the risk.

We chose to include trials that used midazolam and chloral hydrate as comparators because they are widely used in clinical practice (43). In fact, chloral hydrate is recommended by the National Institute for Health and Care Excellence (NICE) 2010 guideline for moderate sedation for painless procedures in children (44). While chloral hydrate is no longer approved by

the United States Food and Drug Administration, it may still be used in other countries. IND provided adequate sedation in 79.7% of children, greater than that of chloral hydrate (75.7%), oral (24.1%) and intranasal midazolam (43.4%). This is consistent with a recent systematic review where IND was superior to oral benzodiazepines in children undergoing anesthetic premedication (16), as well as with another systematic review which found inconsistent evidence of procedural anxiolysis for IN midazolam (11), and with a trial of 300 children undergoing ABR testing where IND sedated significantly more children than chloral hydrate (91% versus 78.5%, respectively) (45). IND may be a safer alternative to chloral hydrate given the latter's propensity to cause respiratory depression (46) and other major adverse effects such as bradycardia, hypotension, and oxygen desaturation (47). In response to evidence that general anesthetics and sedatives in young children may have adverse neurodevelopmental consequences, in 2016, the US Food issued a Drug Safety Communication mandating label changes for all anesthetic gases, and the IV agents propofol, ketamine, barbiturates, and benzodiazepines (48). Dexmedetomidine has been shown to be neuroprotective in animal studies (49) but little long-term data in humans exists. Although IND was reported to produce adequate sedation in more children than IN ketamine (79.7% versus 57.8%), IND was deemed "neutral" versus IN ketamine in all trials that compared the two agents (35, 36, 40). Each trial was small and may not have been sufficiently powered to detect differences in sedation. IND however, may be more suitable than IN ketamine for uncooperative children because fewer IN sprays are required. At 100 mcg/mL, an IND dose of 4 mcg/kg in a 25 kg child would only require two 0.5 mL sprays. Interestingly, in a single study of children undergoing IV insertion, IND was deemed "unfavorable" compared to a combination of IND and oral ketamine, with the latter producing adequate sedation in 80.4% of children (37). The sedative effects of dexmedetomidine may have complemented the well-known

379 analgesic effects of IN ketamine (50, 51) and future studies should explore the sedative potential
380 of this novel therapeutic combination.
381 The most effective non-invasive approach to providing dexmedetomidine appeared to be
382 the IN route. Although informed by only one trial, oral dexmedetomidine was unsuccessful in all
383 cases (41). Oral absorption of dexmedetomidine is possible (52) but its bioavailability is reduced
384 by first-pass metabolism (53). What remains unclear is whether IND administration using an
385 MAD is more efficacious than nasal drops. Li et al. found no difference among children
386 undergoing TTE, a relatively painless procedure (27). In contrast, Xie et al. found lower pain
387 scores during IV insertion using an MAD (38). Nasal drops may result in excess volume entering
388 the oropharynx and more difficult administration in uncooperative patients. Conversely, the
389 MAD takes advantage of the nasal cavity's large mucosal surface area and rich vascular supply
390 (13, 54, 55), resulting in a median bioavailability of 65% (53).
391 Insight into the analgesic potential of IND was limited to two trials that reported lower
392 FLACC scores with IND versus IN midazolam for dental procedures (40) and IND using an
393 MAD versus drops for IV insertion (38). Reduced opioid requirements have been reported with
394 IND in children post-adenotonsillectomy (56) and adults post-hip arthroplasty (57). IV
395 dexmedetomidine has also been shown to reduce opioid requirements in children undergoing
396 scoliosis repair (58) and cardiac surgery (59). However, the proportion of participants deemed as
397 being adequately sedated for painful versus non-painful procedures (61.2% versus 84.1%)
398 suggests that sedation using IND may be improved upon by the addition of a more potent
399 analgesic, perhaps one with sedative properties. Currently, IND as monotherapy is not indicated
400 for severely painful procedures and its analgesic potential appears to be realized in conjunction

401 with local anesthetics (60). Future studies should explore the analgesic potential of IND for
402 acutely painful procedures using rigorous methodology and optimal dosing.
403 The onset and duration of sedation are important considerations in a busy acute care
404 setting. We found wide ranges in onset and duration of IND (7-31 and 41-91.5 minutes,
405 respectively) and data did not support a dose effect. This may reflect heterogeneity in dosing or
406 definitions of sedation but are consistent with previous reports. Among healthy adult males,
407 Iirola et al. reported a median (range) peak plasma concentration at 38 (15-60) minutes and onset
408 of sedation of 30-45 minutes (53). In children, Yuen et al. reported a median (95% CI) onset and
409 duration of sedation of 25 (25 to 30) and 85 (55 to 100) minutes, respectively (61). These results
410 suggest that IND should be administered at least 30 minutes prior to an anxiety-provoking
411 procedure (53). The American Academy of Pediatrics has published guidelines outlining
412 monitoring requirements for children undergoing procedural sedation. Regardless of agent or
413 route of administration, all children should receive comprehensive monitoring for the duration of
414 sedation. This should include, but is not limited to, pulse oximetry and capnography (62).
415 Acceptance of IN administration was only assessed in four trials and not objectively.
416 However, there is good reason to believe that intolerance of nasal sprays is unlikely to preclude
417 IND administration because the drug is tasteless, odorless and painless (53, 54) and reportedly
418 "not noxious to the nasal mucosa" (53, 63), a notable difference from IN midazolam in which
419 discomfort is commonly reported (12, 13).
420 Adverse effects identified in our review such as bradycardia, hypotension, and
421 desaturation were reported across the dosing range and are likely to inform bedside monitoring
422 requirements. For the adverse cardiovascular effects we identified, no resuscitative maneuvers
423 were reported, suggesting they were self-resolving. This is consistent with two paediatric

424 systematic reviews that reported no respiratory compromise with either IND (16) or IV
425 dexmedetomidine (15). In addition, several pediatric studies found that IV dexmedetomidine was
426 associated with bradycardia without hemodynamic instability (15, 54, 58, 64, 65). Nevertheless,
427 it is difficult to know to what degree these occurrences compromised patient care. The most
428 prudent approach would be to limit the use of IND to children without cardiac conduction
429 anomalies, bradycardia, hypotension, or concomitant use of sympatholytic agents. Future studies
430 should define adverse events and corresponding interventions based on published guidelines
431 (66).

432 **Limitations**

433 Our review included a large number of small studies with some methodological
434 shortcomings, the most notable of which was subjective determination of adequacy of sedation.
435 The lack of a consistent and objective determination of this parameter may have led to biased
436 outcome reporting for this and other related outcomes such as onset and duration of sedation.
437 Due to heterogeneity in dosing and indications, it was difficult to appreciate differences in
438 adequate sedation among trials that used validated sedation instruments versus trials that did not.
439 However, based on the classification system outlined by the American College of Emergency
440 Physicians Clinical Policy, we believe that across trials, adequate sedation most closely
441 paralleled *dissociative sedation*, with the caveat that few trials determined the degree of
442 analgesia and no trials assessed amnesia (67). We found large heterogeneity across studies which
443 may be due to different comparators. The funnel plot showed some asymmetry, suggesting the
444 potential for publication or small study bias. As such, we downgraded our certainty of the
445 evidence for some outcomes.

446 **Conclusions**

Our findings suggest that IND is well-tolerated and may provide more effective sedation than midazolam and chloral hydrate for distressing procedures in children. However, the quality of evidence was "low" and larger, more methodologically rigorous trials are needed. The available limited data for painful procedures (mostly IV insertion), suggests that while IND may provide reasonable sedation, it may not provide adequate analgesia as monotherapy. As such, more study is urgently required to understand the role of IND, perhaps in combination with a more widely studied analgesic sedative for painful procedures. Transient cardiovascular adverse effects, without reports of resuscitative intervention, were identified, and more rigorously designed trials with standardized and objective reporting of adverse effects are needed to inform the safe use of IND in children.

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657 **Figure Legends**
658
659 Figure 1 legend.
660 Reasons for exclusion include adult population and/or intravenous dexmedetomidine
661
662 Figure 2 legend.
663 Low risk of bias; Unclear risk of bias; High risk of bias

Figure 3 legend.
CI: Confidence interval; OR: Odds ratio; MD: Mean difference; IN: intranasal

Table 1. Characteristics of included trials

Source, trial design, country, indication for sedation	Age range; (analysis sample size)	Comparisons	Measure of effectiveness of sedation	Results	Summary
Cao 2017 Parallel group RCT China Ophthalmic examination	3-36 months; (n=141)	IN DXM 2 mcg/kg; Oral chloral hydrate 80 mg/kg	Proportion with "Successful sedation to complete the examination" based on the Observer's Assessment of Alertness/Sedation (OAA/S) score ≤ 4	IN DXM 2 mcg/kg 61/71 (85.9%) versus oral chloral hydrate 45/70 (64.3%) (p=0.003)	Favorable for IN DXM 2 mcg/kg versus oral chloral hydrate 80 mg/kg
Chen 2019 Parallel group RCT China Ophthalmic examination	6-24 months (n=100)	IN DXM 2 mcg/kg; IN DXM 3 mcg/kg	Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score	No significant difference in mean (SD) sedation scores between IN DXM 2 mcg/kg [2.6 (2.1)] and IN DXM 3 mcg/kg [2.7 (1.9)] (p>0.05)	Neutral for IN DXM 2 mcg/kg versus IN DXM 3 mcg/kg
Gan 2016 Parallel group RCT China Ophthalmic examination	5-36 months; (n=60)	Following failure of oral or rectal chloral hydrate 80 mg/kg: IN DXM 1 mcg/kg; IN DXM 2 mcg/kg	Proportion with "Successful ophthalmic examination" based on 4-point Likert scale score of 1	IN DXM 2 mcg/kg 28/30 (93.3%) versus IN DXM 1 mcg/kg 20/30 (66.7%) (p=0.02)	Favorable for IN DXM 2 mcg/kg versus IN DXM 1 mcg/kg

Ghai 2017 **Parallel group RCT** **India** **IV insertion and CT**	1-6 years; (n=59)	IN DXM 2.5 mcg/kg; Oral midazolam 0.5 mg/kg	Sedation level based on Groningen Distress Rating Scale (IV insertion) and proportion with "adequate sedation" based on Ramsay Sedation Score ≥ 4 (CT)	Intravenous insertion: Significantly lower median (IQR) scores with IN DXM 2.5 mcg/kg [1 (1)] versus oral midazolam 0.5 mg/kg [2 (1)] (p=0.04) Completion of procedure not reported CT: IN DXM 2.5 mcg/kg 20/30 (67%) versus oral midazolam 0.5 mg/kg 7/29 (24%) (p=0.002)	Favorable for IN DXM 2.5 mcg/kg versus oral midazolam 0.5 mg/kg
Gupta 2017 **Parallel group** **RCT** **India** **IV insertion**	1-8 years; (n=60)	IN DXM 1 mcg/kg; IN midazolam 0.2 mg/kg	Proportion that allowed IV insertion without crying and Observer's Assessment of Alertness/Sedation score ≤ 4	IN DXM 1 mcg/kg 24/30 (80%) versus IN midazolam 0.2 mg/kg 16/30 (53%)	Favorable for IN DXM 1 mcg/kg versus IN midazolam 0.2 mg/kg
Gyanesh 2014 **Parallel group** **RCT** **India** **IV insertion**	1-10 years (n=150)	IN DXM 1 mcg/kg; IN ketamine 5 mg/kg; IN saline	Proportion with satisfactory IV cannulation based on de novo "ease of cannulation score" ≥ 4	IN DXM 1 mcg/kg 20/52 (38%) versus IN ketamine 5 mg/kg 18/52 (35%) (p=0.46) versus IN saline 1/46 (2%) (p<0.01 for both agents versus saline)	Neutral for IN DXM 1 mcg/kg versus IN ketamine 5 mg/kg
Ibrahim 2014 **Parallel group RCT** **Saudi Arabia** **IV insertion and MRI**	4-10 years (n=58)	IN DXM 3 mcg/kg; IN ketamine 7 mg/kg	IV insertion: Proportion with "satisfactory acceptance" based on de novo 4-point scale value ≥ 3 MRI: Sedation failure rate based on the Modified Ramsay Sedation Scale	IV insertion: IN DXM 3 mcg/kg 27/29 (93%) versus IN ketamine 7 mg/kg 27/29 (93%) (p=0.45)[1] MRI: IN DXM 3 mcg/kg 4/29 (14%) versus	Neutral for IN DXM 3 mcg/kg versus IN ketamine 7 mg/kg for both IV insertion and MRI

				IN ketamine 7 mg/kg 6/29 (21%) (p=0.48) All successfully completed MRI	
Li 2014 Parallel group RCT China Diagnostic procedures[2]	1 month to 13 years (n=213)	Following failure of oral chloral hydrate 50 mg/kg: IN DXM 1 mcg/kg, 1.5 mcg/kg, 2 mcg/kg	Adequate sedation based on the Modified Observer's Assessment/ Alertness Scale score from 0-3	IN DXM 1 mcg/kg 56/67 (84%) versus IN DXM 1.5 mcg/kg 66/74 (89%) versus IN DXM 2 mcg/kg 51/53 (96%) (p=0.03[3])	Favorable for higher doses of IN DXM
Li 2016 Parallel group RCT China Transthoracic echocardio-graphy	2-36 months (n=280)	IN DXM 3 mcg/kg using either a mucosal atomizer device (MAD) or nasal drops	"Successful sedation" based on a University of Michigan Sedation Scale score from 2-4	IN DXM 3 mcg/kg via MAD 113/137 (83%) versus drops 120/142 (85%) (p=0.57)	Neutral for IN DXM 3 mcg/kg via MAD versus drops
Miller 2015 Parallel group RCT United States & China Transthoracic echocardio-graphy	3-36 months (n=150)	IN DXM 2 mcg/kg; IN DXM 3 mcg/kg; Chloral hydrate 70 mg/kg	Adequate sedation based on a Ramsay Sedation Score ≥ 3	IN DXM 2 mcg/kg 50/50 (100%) versus IN DXM 3 mcg/kg (48/50) (96%) versus chloral hydrate 70 mg/kg 48/50 (96%) (p=0.36)	Neutral for IN DXM 2 mcg/kg and 3 mcg/kg versus chloral hydrate 70 mg/kg
Neville 2016 Parallel group RCT United States Laceration repair	1-5 years (n=38)	IN DXM 2 mcg/kg; IN midazolam 0.4 mg/kg	"Not anxious" at the time of wound washout based on the Yale Preoperative Anxiety Scale score ≤ 30	IN DXM 2 mcg/kg 7/20 (35%) versus IN midazolam 0.4 mg/kg 1/18 (6%) [OR 3; 95% CI 1-12] Completion of procedure not reported	Neutral for IN DXM 2 mcg/kg versus IN midazolam 0.4 mg/kg

Patel 2018 Parallel group RCT India Dental procedures	4-9 years (n=44)	IN DXM 2.5 mcg/kg; IN DXM 2 mcg/kg; Oral DXM 4 mcg/kg; Oral DXM 5 mcg/kg	"Safe and successful" based on a de novo 5-point scale for response to treatment and adequate sedation, physiologic parameters, and adverse effects with a value ≤ 2	IN DXM 2.5 mcg/kg 9/11 (82%) versus IN DXM 2 mcg/kg 3/11 (27%) versus oral DXM 4 mcg/kg 0/11 (0%) versus oral DXM 5 mcg/kg 0/11 (0%) (p=0.05[3])	Favorable for IN DXM 2.5 mcg/kg versus all other comparators
Qiao 2017 Parallel group RCT China Intravenous insertion	2-5 years (n=135)	IN DXM 2.5 mcg/kg; Oral ketamine 6 mg/kg; IN DXM 2 mcg/kg plus oral ketamine 3 mg/kg	"Successful venous cannulation" based on de novo 5-point sedation scale value ≤ 2	IN DXM 2.5 mcg/kg 20/42 (47%) versus oral ketamine 6 mg/kg 28/41 (68%) versus IN DXM 2 mcg/kg plus oral ketamine 3 mg/kg 33/41 (80%) (p=0.006[3])	Unfavorable for IN DXM 2.5 mg/kg versus combination of IN DXM 2 mcg/kg plus oral ketamine 3 mg/kg and oral ketamine 6 mg/kg
Reynolds 2016 Parallel group RCT United States Auditory brainstem response testing	6 months-8 years (n=85)	IN DXM 3 mcg/kg; Chloral hydrate 50 mg/kg	"Satisfactory sedation" based on ability of audiologist to complete the procedure by placing electrodes within 30 minutes	IN DXM 3 mcg/kg 39/44 (89%) versus chloral hydrate 50 mg/kg 27/41 (66%) (p=0.18)	Favorable for IN DXM 3 mcg/kg versus chloral hydrate 50 mg/kg
Surendar 2014 Parallel group RCT India Dental procedures	4-14 years (n=84)	IN DXM 1.5 mcg/kg; IN DXM 1 mcg/kg; IN midazolam 0.2 mg/kg; IN ketamine 5 mg/kg	"Satisfactory sedation" for the first 30 minutes of the procedure based on a de novo 5-point scale (4 or 5)	IN DXM 1.5 mcg/kg 18/21 (86%) versus IN DXM 1 mcg/kg 17/21 (81%) versus IN midazolam 0.2 mg/kg 13/21 (62%) versus IN ketamine 5 mg/kg 14/21 (67%) (p=0.24[3])	Neutral for IN DXM 1.5 mcg/kg and IN DXM 1 mcg/kg versus IN midazolam 0.2 mg/kg and IN ketamine 5 mg/kg
Tug 2015 Parallel group RCT Turkey MRI	1-10 years (n=60)	IN DXM 3 mcg/kg; IN DXM 4 mcg/kg	"Adequate sedation" based on Ramsay Sedation Score ≥ 5 and no need for rescue sedation for MRI at 45 minutes	IN DXM 3 mcg/kg 9/30 (30%) versus IN DXM 4 mcg/kg 21/30 (70%) (p=0.002)	Favorable for IN DXM 4 mcg/kg versus IN DXM 3 mcg/kg

Xie 2015 **Parallel group RCT** **China** **IV insertion**	2-5 years (n=106)	IN DXM 2 mcg/kg using mucosal atomizer device; IN DXM 2 mcg/kg using drops	Response to IV insertion based on Faces, Legs, Activity, Cry, Consolability (FLACC) score	Median (IQR) FLACC score for IN DXM 2 mcg/kg using mucosal atomizer device was 1 (3.5) versus IN DXM 2 mcg/kg using drops was 3 (4) (p=0.02) All participants had completed IV insertions	Favorable for IN DXM 2 mcg/kg using mucosal atomizer device versus IN DXM 2 mcg/kg using drops
Yuen 2017 **Parallel group RCT** **China** **CT**	Age range not specified (n=196)	IN DXM 3 mcg/kg; Oral chloral hydrate 50mg/kg	"Adequate sedation" based on University of Michigan Sedation Scale score ≥ 3	IN DXM 3 mcg/kg 64/87 (74%) versus oral chloral hydrate 81/107 (76%) (p=0.74)	Neutral for IN DXM 3 mcg/kg versus oral chloral hydrate 50 mg/kg
Zhang 2016 **Parallel group RCT** **China** **MRI**	1-6 months (n=150)	Following failure of oral chloral hydrate 50 mg/kg: IN DXM 1 mcg/kg; IN DXM 2 mcg/kg; Oral chloral hydrate 25 mg/kg	"Successful sedation" based on the Modified Observer's Assessment of Alertness/Sedation Scale score ≤ 3	IN DXM 1 mcg/kg 47/50 (94%) versus IN DXM 2 mcg/kg 49/50 (98%) versus oral chloral hydrate 25 mg/kg 40/50 (80%) (p<0.01)	Favorable for IN DXM 1 mcg/kg and 2 mcg/kg versus oral chloral hydrate 25 mg/kg

CT computed tomography; DXM dexmedetomidine; IN intranasal; IQR interquartile range; IV intravenous; MRI magnetic resonance imaging; RCT randomized controlled trial
[1]p value reflects between-group differences in overall 4-point scale
Includes computed tomography, auditory brainstem testing; visual evoked potentials
[3]p value reflects overall difference between groups

Figure 1. Study Flow Diagram

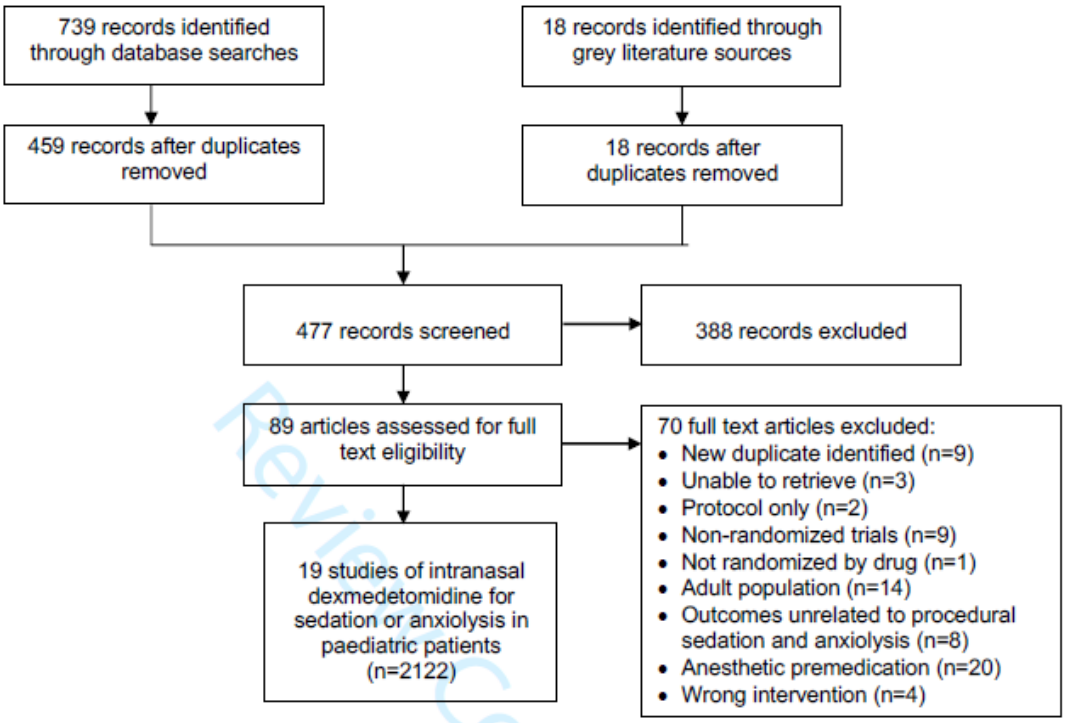


Figure 2. Review authors' judgements about each risk of bias item presented as percentages across all included studies.

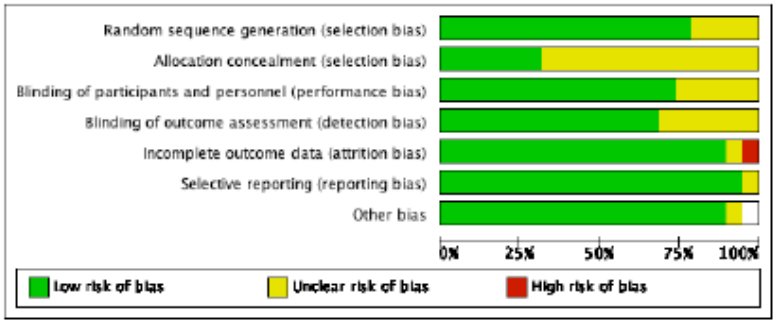


Figure 3. GRADE Evidence Profile

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intranasal dexmedetomidine	other sedatives	Relative (95% CI)	Absolute (95% CI)		
Adequacy of Sedation												
18	randomized trials	not serious [a]	serious [b]	serious [c]	not serious	none	1086/1382 (79.7%)	398/622 (64.0%)	not pooled	see comment	⨁⨁◯◯ LOW	CRITICAL
Need for Additional Sedation												
5	randomized trials	not serious [a]	not serious	serious [c]	not serious	none	22/223 (9.9%)	47/167 (28.1%)	not pooled	see comment	⨁⨁⨁◯ MODERATE	CRITICAL
Onset of Sedation												
11	randomized trials	serious [d]	serious [e]	not serious	not serious	none	IN dexmedetomidine range 7-31 minutes; IN comparator range 7-44.2 minutes				⨁⨁◯◯ LOW	IMPORTANT
Duration of Sedation												
6	randomized trials	serious [d]	not serious	not serious	not serious	none	IN dexmedetomidine range 41-91.5 minutes; IN comparator range 77-85.9 minutes				⨁⨁⨁◯ MODERATE	IMPORTANT
Length of Stay												
4	randomized trials	not serious	not serious	not serious	not serious	none	IN dexmedetomidine range 76.8-156 minutes; IN comparator range 95-144 minutes				⨁⨁⨁⨁ HIGH	IMPORTANT
Analgesia												
1	randomized trials	not serious	serious [f]	not serious	serious [g]	none	Overall significant difference in the mean (SD) FLACC score during dental procedures between IND 1 mcg/kg [3.8 (0.8)], IND 1.5 mcg/kg [3.7 (0.9)], IN midazolam [5.6 (1.1)], and IN ketamine [3.5 (0.7)] (p<0.001).				⨁⨁◯◯ LOW	IMPORTANT
Adverse Effects												
18	randomized trials	serious [a,h]	not serious	not serious	not serious	none	67/727 (9.2%)	98/591 (16.6%)	not pooled	see comment	⨁⨁⨁◯ MODERATE	CRITICAL
Acceptance of IN Administration												
4	randomized trials	serious [k]	not serious	not serious	not serious	none	IN dexmedetomidine well accepted by 199/264 (75.4%) participants with no reports of aborting administration due to refusal. One study reported IN midazolam well accepted by 42/42 (100%) of participants.				⨁⨁⨁◯ MODERATE	IMPORTANT

CI: Confidence Interval; OR: Odds ratio; MD: Mean difference

Explanations

a. We chose not to downgrade for allocation concealment (selection bias) because although most trials were judged to have an unclear risk of bias, in all cases this was due to insufficient details provided
b. Significant heterogeneity (I-squared=72%) partially explained by different comparators

c. Use of a non-standardized tool to determine level and adequacy of sedation in at least one study limits the degree to which the results can be applied broadly
d. Use of non-standardized tools to define the onset of sedation was prevalent across trials
e. Downgraded for consistency due to the large range in this outcome, which was in turn likely due to heterogeneity in measurement instruments, dose, and comparators
f. Unable to assess given only one study reporting this outcome
g. Total sample size < 200 participants
h. Li et al. was judged to have high risk of bias for incomplete outcome data because 14/67 participants in the IND 2 mcg/kg arm withdrew post-randomization and did not return to the sedation centre
i. Surendar et al. did not report adverse effects but reported vital signs during sedation that appeared to be within physiologic parameters and the risk of bias was deemed to be unclear
j. Adverse effects were not defined using standardized or objective criteria
k. Use of non-standardized tools to assess tolerability of IN sprays limits the degree to which the results can be applied broadly

Table 1. Characteristics and results of included studies

Source, trial design, country, indication for sedation	Age range; (analysis sample size)	Comparisons	Measure of effectiveness of sedation	Results	Summary
Cao 2017 Parallel group RCT China Ophthalmic examination	3-36 months; (n=141)	IN DXM 2 mcg/kg; Oral chloral hydrate 80 mg/kg	Proportion with "Successful sedation to complete the examination" based on the Observer's Assessment of Alertness/Sedation (OAA/S) score ≤ 4	IN DXM 2 mcg/kg 61/71 (85.9%) versus oral chloral hydrate 45/70 (64.3%) (p=0.003)	Favorable for IN DXM 2 mcg/kg versus oral chloral hydrate 80 mg/kg
Chen 2019 Parallel group RCT China Ophthalmic examination	6-24 months (n=100)	IN DXM 2 mcg/kg; IN DXM 3 mcg/kg	Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score with successful sedation 0-3	No significant difference in mean (SD) sedation scores between IN DXM 2 mcg/kg [2.6 (2.1)] and IN DXM 3 mcg/kg [2.7 (1.9)] (p>0.05) IND 2 mcg/kg: 49/50 completed all procedures IND 3 mcg/kg: 50/50 completed all procedures	Neutral for IN DXM 2 mcg/kg versus IN DXM 3 mcg/kg
Gan 2016 Parallel group RCT China Ophthalmic examination	5-36 months; (n=60)	Following failure of oral or rectal chloral hydrate 80 mg/kg: IN DXM 1 mcg/kg; IN DXM 2 mcg/kg	Proportion with "Successful ophthalmic examination" based on 4-point Likert scale score of 1	IN DXM 2 mcg/kg 28/30 (93.3%) versus IN DXM 1 mcg/kg 20/30 (66.7%) (p=0.02)	Favorable for IN DXM 2 mcg/kg versus IN DXM 1 mcg/kg
Ghai 2017 Parallel group RCT India IV insertion and CT	1-6 years; (n=59)	IN DXM 2.5 mcg/kg; Oral midazolam 0.5 mg/kg	Sedation level based on Groningen Distress Rating Scale (IV insertion) and proportion with "adequate	Intravenous insertion: Significantly lower median (IQR) scores with IN DXM 2.5 mcg/kg [1 (1)] versus oral midazolam 0.5 mg/kg [2 (1)] (p=0.04) Completion of procedure not reported CT:	Favorable for IN DXM 2.5 mcg/kg versus oral midazolam 0.5 mg/kg

Commented [CP1]: Added new study from July 26, 2019 search results

			sedation" based on Ramsay Sedation Score ≥ 4 (CT)	IN DXM 2.5 mcg/kg 20/30 (67%) versus oral midazolam 0.5 mg/kg 7/29 (24%) (p=0.002)	
Gupta 2017 Parallel group RCT India IV insertion	1-8 years; (n=60)	IN DXM 1 mcg/kg; IN midazolam 0.2 mg/kg	Proportion that allowed IV insertion without crying and Observer's Assessment of Alertness/Sedation score ≤ 4	IN DXM 1 mcg/kg 24/30 (80%) versus IN midazolam 0.2 mg/kg 16/30 (53%)	Favorable for IN DXM 1 mcg/kg versus IN midazolam 0.2 mg/kg
Gyanesh 2014 Parallel group RCT India IV insertion	1-10 years (n=150)	IN DXM 1 mcg/kg; IN ketamine 5 mg/kg; IN saline	Proportion with satisfactory IV cannulation based on de novo "ease of cannulation score" ≥ 4	IN DXM 1 mcg/kg 20/52 (38%) versus IN ketamine 5 mg/kg 18/52 (35%) (p=0.46) versus IN saline 1/46 (2%) (p<0.01 for both agents versus saline)	Neutral for IN DXM 1 mcg/kg versus IN ketamine 5 mg/kg
Ibrahim 2014 Parallel group RCT Saudi Arabia IV insertion and MRI	4-10 years (n=58)	IN DXM 3 mcg/kg; IN ketamine 7 mg/kg	IV insertion: Proportion with "satisfactory acceptance" based on de novo 4-point scale value ≥ 3 MRI: Sedation failure rate based on the Modified Ramsay Sedation Scale	IV insertion: IN DXM 3 mcg/kg 27/29 (93%) versus IN ketamine 7 mg/kg 27/29 (93%) (p=0.45)[1] MRI: IN DXM 3 mcg/kg 4/29 (14%) versus IN ketamine 7 mg/kg 6/29 (21%) (p=0.48) All successfully completed MRI	Neutral for IN DXM 3 mcg/kg versus IN ketamine 7 mg/kg for both IV insertion and MRI
Li 2014 Parallel group RCT China Diagnostic procedures[2]	1 month to 13 years (n=213)	Following failure of oral chloral hydrate 50 mg/kg: IN DXM 1 mcg/kg, 1.5 mcg/kg, 2 mcg/kg	Adequate sedation based on the Modified Observer's Assessment/ Alertness Scale score from 0-3	IN DXM 1 mcg/kg 56/67 (84%) versus IN DXM 1.5 mcg/kg 66/74 (89%) versus IN DXM 2 mcg/kg 51/53 (96%) (p=0.03[3])	Favorable for higher doses of IN DXM
Li 2016 Parallel group RCT China Transthoracic echocardio-graphy	2-36 months (n=280)	IN DXM 3 mcg/kg using either a mucosal atomizer device (MAD) or nasal drops	"Successful sedation" based on a University of Michigan Sedation Scale score from 2-4	IN DXM 3 mcg/kg via MAD 113/137 (83%) versus drops 120/142 (85%) (p=0.57)	Neutral for IN DXM 3 mcg/kg via MAD versus drops
Miller 2015 Parallel group RCT United States & China Transthoracic echocardio-graphy	3-36 months (n=150)	IN DXM 2 mcg/kg; IN DXM 3 mcg/kg; Chloral hydrate 70 mg/kg	Adequate sedation based on a Ramsay Sedation Score ≥ 3	IN DXM 2 mcg/kg 50/50 (100%) versus IN DXM 3 mcg/kg (48/50) (96%) versus chloral hydrate 70 mg/kg 48/50 (96%) (p=0.36)	Neutral for IN DXM 2 mcg/kg and 3 mcg/kg versus chloral hydrate 70 mg/kg
Neville 2016 Parallel group RCT United States Laceration repair	1-5 years (n=38)	IN DXM 2 mcg/kg; IN midazolam 0.4 mg/kg	"Not anxious" at the time of wound washout based on the Yale Preoperative Anxiety Scale score ≤ 30	IN DXM 2 mcg/kg 7/20 (35%) versus IN midazolam 0.4 mg/kg 1/18 (6%) [OR 3; 95% CI 1-12] Completion of procedure not reported	Neutral for IN DXM 2 mcg/kg versus IN midazolam 0.4 mg/kg

Patel 2018 Parallel group RCT India Dental procedures	4-9 years (n=44)	IN DXM 2.5 mcg/kg; IN DXM 2 mcg/kg; Oral DXM 4 mcg/kg; Oral DXM 5 mcg/kg	"Safe and successful" based on a de novo 5-point scale for response to treatment and adequate sedation, physiologic parameters, and adverse effects with a value ≤ 2	IN DXM 2.5 mcg/kg 9/11 (82%) versus IN DXM 2 mcg/kg 3/11 (27%) versus oral DXM 4 mcg/kg 0/11 (0%) versus oral DXM 5 mcg/kg 0/11 (0%) (p=0.05[J])	Favorable for IN DXM 2.5 mcg/kg versus all other comparators
Qiao 2017 Parallel group RCT China Intravenous insertion	2-5 years (n=135)	IN DXM 2.5 mcg/kg; Oral ketamine 6 mg/kg; IN DXM 2 mcg/kg plus oral ketamine 3 mg/kg	"Successful venous cannulation" based on de novo 5-point sedation scale value ≤ 2	IN DXM 2.5 mcg/kg 20/42 (47%) versus oral ketamine 6 mg/kg 28/41 (68%) versus IN DXM 2 mcg/kg plus oral ketamine 3 mg/kg 33/41 (80%) (p=0.006[J])	Unfavorable for IN DXM 2.5 mg/kg versus combination of IN DXM 2 mcg/kg plus oral ketamine 3 mg/kg and oral ketamine 6 mg/kg
Reynolds 2016 Parallel group RCT United States Auditory brainstem response testing	6 months-8 years (n=85)	IN DXM 3 mcg/kg; Chloral hydrate 50 mg/kg	"Satisfactory sedation" based on ability of audiologist to complete the procedure by placing electrodes within 30 minutes	IN DXM 3 mcg/kg 39/44 (89%) versus chloral hydrate 50 mg/kg 27/41 (66%) (p=0.18)	Favorable for IN DXM 3 mcg/kg versus chloral hydrate 50 mg/kg

Surendar 2014 Parallel group RCT India Dental procedures	4-14 years (n=84)	IN DXM 1.5 mcg/kg; IN DXM 1 mcg/kg; IN midazolam 0.2 mg/kg; IN ketamine 5 mg/kg	"Satisfactory sedation" for the first 30 minutes of the procedure based on a de novo 5-point scale (4 or 5)	IN DXM 1.5 mcg/kg 18/21 (86%) versus IN DXM 1 mcg/kg 17/21 (81%) versus IN midazolam 0.2 mg/kg 13/21 (62%) versus IN ketamine 5 mg/kg 14/21 (67%) (p=0.24[J])	Neutral for IN DXM 1.5 mcg/kg and IN DXM 1 mcg/kg versus IN midazolam 0.2 mg/kg and IN ketamine 5 mg/kg
Tug 2015 Parallel group RCT Turkey MRI	1-10 years (n=60)	IN DXM 3 mcg/kg; IN DXM 4 mcg/kg	"Adequate sedation" based on Ramsay Sedation Score ≥ 5 and no need for rescue sedation for MRI at 45 minutes	IN DXM 3 mcg/kg 9/30 (30%) versus IN DXM 4 mcg/kg 21/30 (70%) (p=0.002)	Favorable for IN DXM 4 mcg/kg versus IN DXM 3 mcg/kg
Xie 2015 Parallel group RCT China IV insertion	2-5 years (n=106)	IN DXM 2 mcg/kg using mucosal atomizer device; IN DXM 2 mcg/kg using drops	Response to IV insertion based on Faces, Legs, Activity, Cry, Consolability (FLACC) score	Median (IQR) FLACC score for IN DXM 2 mcg/kg using mucosal atomizer device was 1 (3.5) versus IN DXM 2 mcg/kg using drops was 3 (4) (p=0.02) All participants had completed IV insertions	Favorable for IN DXM 2 mcg/kg using mucosal atomizer device versus IN DXM 2 mcg/kg using drops
Yuen 2017 Parallel group RCT China CT	Age range not specified (n=196)	IN DXM 3 mcg/kg; Oral chloral hydrate 50 mg/kg	"Adequate sedation" based on University of Michigan Sedation Scale score ≥ 3	IN DXM 3 mcg/kg 64/87 (74%) versus oral chloral hydrate 81/107 (76%) (p=0.74)	Neutral for IN DXM 3 mcg/kg versus oral chloral hydrate 50 mg/kg

Zhang 2016 Parallel group RCT China MRI	1-6 months (n=150)	Following failure of oral chloral hydrate 50 mg/kg: IN DXM 1 mcg/kg; IN DXM 2 mcg/kg; Oral chloral hydrate 25 mg/kg	"Successful sedation" based on the Modified Observer's Assessment of Alertness/Sedation Scale score ≤ 3	IN DXM 1 mcg/kg 47/50 (94%) versus IN DXM 2 mcg/kg 49/50 (98%) versus oral chloral hydrate 25 mg/kg 40/50 (80%) (p<0.01)	Favorable for IN DXM 1 mcg/kg and 2 mcg/kg versus oral chloral hydrate 25 mg/kg

CT computed tomography; DXM dexmedetomidine; IN intranasal; IQR interquartile range; IV intravenous; MRI magnetic resonance imaging; RCT randomized controlled trial

[1]P value reflects between-group differences in overall 4-point scale

Includes computed tomography, auditory brainstem testing, visual evoked potentials

[2]P value reflects overall difference between groups

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Figure 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 4
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	n/a

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Search as of July 26, 2019

CINAHL:

#	Query	Results
S38	S36 AND S37	39
S37	S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35	2,817
S36	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12	1,566
S35	(MH "Administration, Intranasal")	2,371
S34	medication*, nasal	80
S33	nasal medication*	80
S32	medication*, intra-nasal	0
S31	intra-nasal medication*	0
S30	medication*, intranasal	49
S29	intranasal medication*	49
S28	instillation*, nasal	22
S27	nasal instillation*	22
S26	instillation*, intra-nasal	0
S25	intra-nasal instillation*	0
S24	instillation*, intranasal	27
S23	intranasal instillation	27
S22	administration*, nasal	301
S21	nasal administration*	301
S20	intra-nasal drug administration*	0
S19	intra-nasal administration*	2
S18	drug administration*, intra-nasal	0
S17	administration*, intra-nasal	0
S16	intranasal drug administration*	23
S15	intranasal administration*	2,517
S14	drug administration*, intranasal	27
S13	administration*, intranasal	2,517

S12	sileo	1
S11	sedadex	0
S10	primadex	0
S9	dexdor	3
S8	dexdomitor	0
S7	cepedex	0
S6	precedex	14
S5	"mpv1440"	0
S4	hydrochloride, dexmedetomidine	13
S3	"mpv 1440"	0
S2	dexmedetomidine hydrochloride	13
S1	"Dexmedetomidine"	1,564

Database(s): **Embase Classic+Embase** 1947 to 2019 July 25
Search Strategy:

#	Searches	Results
1	dexmedetomidine/	9901
2	dexmedetomidine.mp.	10149
3	dexmedetomidine hydrochloride.mp.	95
4	hydrochloride, dexmedetomidine.mp.	3
5	mpv 1440.mp.	4
6	mpv1440.mp.	0
7	precedex.mp.	450
8	cepedex.mp.	0
9	dexdomitor.mp.	123
10	dexdor.mp.	41
11	primadex.mp.	2
12	sedadex.mp.	0
13	sileo.mp.	6
14	intranasal drug administration/	14768
15	administration*, intranasal.mp.	84
16	drug administration*, intranasal.mp.	4

17	intranasal administration*.mp.	4312
18	intranasal drug administration*.mp.	39833
19	administration*, intra-nasal.mp.	3
20	drug administration*, intra-nasal.mp.	1
21	intra-nasal administration*.mp.	47
22	intra-nasal drug administration*.mp.	0
23	nasal administration*.mp.	1394
24	administration*, nasal.mp.	29
25	intranasal instillation*.mp.	977
26	instillation*, intranasal.mp.	3
27	intra-nasal instillation*.mp.	18
28	instillation*, intra-nasal.mp.	0
29	nasal instillation*.mp.	361
30	instillation*, nasal.mp.	3
31	intranasal medication*.mp.	94
32	medication*, intranasal.mp.	11
33	intra-nasal medication*.mp.	1
34	medication*, intra-nasal.mp.	0
35	nasal medication*.mp.	73
36	medication*, nasal.mp.	21
37	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	10153
38	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	42030
39	37 and 38	269

Database(s): **Ovid MEDLINE(R) ALL** 1946 to July 25, 2019
Search Strategy:

#	Searches	Results
1	dexmedetomidine/	3137
2	dexmedetomidine.mp.	5317
3	dexmedetomidine hydrochloride.mp.	60
4	hydrochloride, dexmedetomidine.mp.	1

5	mpv 1440.mp.	3
6	mpv1440.mp.	0
7	precedex.mp.	31
8	cepedex.mp.	0
9	dexdomitor.mp.	1
10	dexdor.mp.	8
11	primadex.mp.	0
12	sedadex.mp.	0
13	sileo.mp.	2
14	administration*, intranasal.mp.	14057
15	drug administration*, intranasal.mp.	1
16	intranasal administration*.mp.	3262
17	intranasal drug administration*.mp.	45
18	administration*, intra-nasal.mp.	0
19	drug administration*, intra-nasal.mp.	0
20	intra-nasal administration*.mp.	28
21	intra-nasal drug administration*.mp.	0
22	nasal administration*.mp.	985
23	administration*, nasal.mp.	24
24	intranasal instillation*.mp.	676
25	instillation*, intranasal.mp.	2
26	intra-nasal instillation*.mp.	10
27	instillation*, intra-nasal.mp.	0
28	nasal instillation*.mp.	234
29	instillation*, nasal.mp.	3
30	intranasal medication*.mp.	67
31	medication*, intranasal.mp.	7
32	intra-nasal medication*.mp.	1
33	medication*, intra-nasal.mp.	0
34	nasal medication*.mp.	55
35	medication*, nasal.mp.	13

36	Administration, Intranasal/	14038
37	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	5323
38	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	16415
39	37 and 38	96

Scopus: 301 results

ALL((Dexmedetomidine OR "dexmedetomidine hydrochloride" OR "hydrochloride, dexmedetomidine" OR "mpv 1440" OR mpv-1440 OR mpv1440 OR precedex OR cepedex OR dexdomitor OR dexdor OR primadex OR sedadex OR sileo) AND ("administration, intranasal" OR "administrations, intranasal" OR "drug administration, intranasal" OR "drug administrations, intranasal" OR "intranasal administration" OR "intranasal administrations" OR "intranasal drug administration" OR "intranasal drug administrations" OR "administration, intra-nasal" OR "administrations, intra-nasal" OR "drug administration, intra-nasal" OR "drug administrations, intra-nasal" OR "intra-nasal administration" OR "intra-nasal administrations" OR "intra-nasal drug administration" OR "intra-nasal drug administrations" OR "nasal administration" OR "nasal administrations" OR "administration, nasal" OR "administrations, nasal" OR "intranasal instillation" OR "intranasal instillations" OR "instillation, intranasal" OR "instillations, intranasal" OR "intra-nasal instillation" OR "intra-nasal instillations" OR "instillation, intra-nasal" OR "instillations, intra-nasal" OR "nasal instillation" OR "nasal instillations" OR "instillation, nasal" OR "instillations, nasal" OR "intranasal medication" OR "intranasal medications" OR "medication, intranasal" OR "medications, intranasal" OR "intra-nasal medication" OR "intra-nasal medications" OR "medication, intra-nasal" OR "medications, intra-nasal" OR "nasal medication" OR "nasal medications" OR "medication, nasal" OR "medications, nasal"))

Web of Science: 31 results

TS=((Dexmedetomidine OR "dexmedetomidine hydrochloride" OR "hydrochloride, dexmedetomidine" OR "mpv 1440" OR mpv-1440 OR mpv1440 OR precedex OR cepedex OR dexdomitor OR dexdor OR primadex OR sedadex OR sileo) AND ("administration, intranasal" OR "administrations, intranasal" OR "drug administration, intranasal" OR "drug administrations, intranasal" OR "intranasal administration" OR "intranasal administrations" OR "intranasal drug administration" OR "intranasal drug administrations" OR "administration, intra-nasal" OR "administrations, intra-nasal" OR "drug administration, intra-nasal" OR "drug administrations, intra-nasal" OR "intra-nasal administration" OR "intra-nasal administrations" OR "intra-nasal drug administration" OR "intra-nasal drug administrations" OR "nasal administration" OR "nasal administrations" OR "administration, nasal" OR "administrations, nasal" OR "intranasal instillation" OR "intranasal instillations" OR "instillation, intranasal" OR "instillations, intranasal" OR "intra-nasal instillation" OR "intra-nasal instillations" OR "instillation, intra-

nasal" OR "instillations, intra-nasal" OR "nasal instillation" OR "nasal instillations" OR "instillation, nasal" OR "instillations, nasal" OR "intranasal medication" OR "intranasal medications" OR "medication, intranasal" OR "medications, intranasal" OR "intra-nasal medication" OR "intra-nasal medications" OR "medication, intra-nasal" OR "medications, intra-nasal" OR "nasal medication" OR "nasal medications" OR "medication, nasal" OR "medications, nasal"))
Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI.

GRAY LITERATURE SEARCH

Clinical Trials Registries

Search: Dexmedetomidine AND (intranasal OR intra-nasal)

UK Clinical Trials Gateway

0 Results

ISRCTN Register

0 Results

HSRProj

0 Results

NIH Reporter

0 Results

PhRMA Clinical Study Results Database

0 Results

Eli Lilly and Company Clinical Trial Registry

0 Results

Roche Clinical Study Register

0 Results

GlaxoSmithKline Clinical Study Register

0 Results

ClinicalTrials.gov

8 Results

Study 1:
Title: The Clinical Research of Intranasal Dexmedetomidine Used in Plastic Surgery of Children
Recruitment: Unknown status
Study Results: No Results Available
Conditions: The Efficacy and Safety of Intranasal Dexmedetomidine
Interventions: Drug: Normal saline,1 milliliter|Drug: Dexmedetomidine 1 μg.kg-1,1 milliliter|Drug: Dexmedetomidine 2μg.kg-1,1 milliliter|Drug: Anesthesia induction, 8% sevoflurane|Drug: Anesthesia maintenance, 2%~3% sevoflurane,fentanyl
URL: https://ClinicalTrials.gov/show/NCT02222636

Study 2:
Title: Efficacy and Optimal Dose Selection of Intranasal Dexmedetomidine During Breast Lumpectomy Under Local Anaesthesia
Recruitment: Completed
Study Results: No Results Available
Conditions: Intranasal Dexmedetomidine Breast Cancer Local Anaesthesia
Interventions: Drug: 0.9% saline|Drug: dexmedetomidine 1μg.kg-1|Drug: dexmedetomidine 1.5μg.kg-1|Drug: Dexmedetomidine 2μg.kg-1
URL: https://ClinicalTrials.gov/show/NCT02675049

Study 3:
Title: Safety and Efficacy of Intranasal Dexmedetomidine
Recruitment: Not yet recruiting
Study Results: No Results Available
Conditions: Safety and Efficacy of Intranasal Dexmedetomidine
Interventions: Drug: Dexmedetomidine|Drug: Midazolam Hydrochloride|Drug: Nitrous Oxide
URL: https://ClinicalTrials.gov/show/NCT02985697

Study 4:
Title: Intranasal Dexmedetomidine Sedation in Children for Non-painful Procedures
Recruitment: Not yet recruiting
Study Results: No Results Available
Conditions: Dexmedetomidine|Sedation
Interventions: Drug: Intranasal dexmedetomidine
URL: https://ClinicalTrials.gov/show/NCT03220880

Study 5:
Title: Sedation and Physiological Effects of Intranasal Dexmedetomidine in Severe COPD

Recruitment: Completed
Study Results: No Results Available
Conditions: COPD|Sedation|Dexmedetomidine
Interventions: Drug: Intranasal dexemdetomidine (IN-DEX)
URL: https://ClinicalTrials.gov/show/NCT02211118

Study 6:
Title: Intranasal Dexmedetomidine Premedication
Recruitment: Completed
Study Results: Has Results
Conditions: Benign Neoplasm of Vocal Fold - Glottis
Interventions: Drug: Dexmedetomidine|Drug: placebo
URL: https://ClinicalTrials.gov/show/NCT02108171

Study 7:
Title: Intranasal Dexmedetomidine Sedation for Pediatric CT Imaging
Recruitment: Unknown status
Study Results: No Results Available
Conditions: Traumatic Brain Injury|Children
Interventions: Drug: Dexmedetomidine
URL: https://ClinicalTrials.gov/show/NCT01900405

Study 8:
Title: Bioavailability of Dexmedetomidine After Intranasal Administration
Recruitment: Completed
Study Results: No Results Available
Conditions: Sedation
Interventions: Drug: Intravenous dexmedetomidine|Drug: Intranasal dexmedetomidine
URL: https://ClinicalTrials.gov/show/NCT00837187

Study 9:
Title: Intranasal Dexmedetomidine vs Intranasal Midazolam as Anxiolysis Prior to Pediatric Laceration Repair
Recruitment: Completed
Study Results: Has Results
Conditions: Laceration|Anxiety
Interventions: Drug: Dexmedetomidine|Drug: Midazolam
URL: https://ClinicalTrials.gov/show/NCT02168439

Study 10:
Title: Intranasal Dexmedetomidine vs Midazolam-ketamine Combination for Premedication of Pediatric Patients
Recruitment: Completed

Study Results: No Results Available
Conditions: Premedication|Oculocardiac Reflex
Interventions: Drug: Dexmedetomidine|Drug: Ketamine
URL: https://ClinicalTrials.gov/show/NCT02072083

Study 11:
Title: Intranasal Dexmedetomidine Sedation During Intra-articular Joint Injections in Pediatric Population
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Juvenile Idiopathic Arthritis|Joint Inflammation
Interventions: Drug: Dexmedetomidine|Drug: Sedatives/Hypnotics,Other
URL: https://ClinicalTrials.gov/show/NCT03069638

Study 12:
Title: Placebo Controlled Evaluation of Sedation and Physiological Response to Intranasal Dexmedetomidine in Severe COPD
Recruitment: Not yet recruiting
Study Results: No Results Available
Conditions: COPD
Interventions: Drug: IN-DEX 1.0 mcg/kg, intranasal saline|Drug: IN-DEX 1.5 mcg/kg, intranasal saline|Drug: Placebo - Saline
URL: https://ClinicalTrials.gov/show/NCT02773797

Study 13:
Title: A Comparison of Two Doses of Intranasal Dexmedetomidine for Premedication in Children
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Anxiety, Separation
Interventions: Drug: Dexmedetomidine
URL: https://ClinicalTrials.gov/show/NCT02459509

Study 14:
Title: Pharmacokinetic Study of Dexmedetomidine After Intra-nasal Dosing in Children
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Heart Disease
Interventions: Drug: Dexmedetomidine|Drug: Dexmedetomidine|Drug: Dexmedetomidine
URL: https://ClinicalTrials.gov/show/NCT02836431

Study 15:
Title: Intranasal Dexmedetomidine for Procedural Pain Management in Elderly Adults in Palliative Care
Recruitment: Not yet recruiting
Study Results: No Results Available
Conditions: Analgesia|Sedation|Anxiolysis
Interventions: Drug: Opioids|Drug: Dexmedetomidine|Drug: Placebo
URL: https://ClinicalTrials.gov/show/NCT03151863

Study 16:
Title: Premedication With Intranasal Dexmedetomidine or Midazolam for Prevention of Emergence Agitation in Children
Recruitment: Not yet recruiting
Study Results: No Results Available
Conditions: Emergence Delirium
Interventions: Drug: Dexmedetomidine|Drug: Midazolam oral solution|Drug: Oral saline|Drug: Nasal saline
URL: https://ClinicalTrials.gov/show/NCT03171740

Study 17:
Title: Intranasal Dexmedetomidine Premedication in Children
Recruitment: Completed
Study Results: Has Results
Conditions: Preoperative Sedation
Interventions: Drug: Midazolam|Drug: Dexmedetomidine
URL: https://ClinicalTrials.gov/show/NCT02250703

Study 18:
Title: Intranasal Dexmedetomidine Sedation for Ophthalmic Examinations in Children
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Sniffs Drugs
Interventions: Drug: intranasal dexmedetomidine
URL: https://ClinicalTrials.gov/show/NCT02077712

Study 19:
Title: Sedation Using Intranasal Dexmedetomidine in Upper Gastrointestinal Endoscopy
Recruitment: Completed
Study Results: No Results Available
Conditions: Gastrointestinal Disease
Interventions: Drug: Dexmedetomidine

URL: https://ClinicalTrials.gov/show/NCT01887184

Study 20:
Title: Comparison of Two Doses of Intranasal Dexmedetomidine as Premedication in Children
Recruitment: Unknown status
Study Results: No Results Available
Conditions: Patient Between 1-8 Years Old Undergoing Elective Surgery at Queen Mary Hospital
Interventions: Drug: Dexmedetomidine
URL: https://ClinicalTrials.gov/show/NCT01065701

Study 21:
Title: Placebo-Controlled Evaluation of Intranasal Dexmedetomidine for Postoperative Analgesia Following Bunionectomy Surgery
Recruitment: Completed
Study Results: Has Results
Conditions: Pain, Post-operative
Interventions: Drug: Intranasal Dexmedetomidine|Drug: Intranasal Placebo
URL: https://ClinicalTrials.gov/show/NCT02284243

Study 22:
Title: A Trial Of Oral Chloral Hydrate Versus Intranasal Dexmedetomidine For Sedated Abr Exams
Recruitment: Completed
Study Results: Has Results
Conditions: Sedation
Interventions: Drug: Chloral Hydrate|Drug: Dexmedetomidine|Other: Oral placebo|Other: Intranasal placebo
URL: https://ClinicalTrials.gov/show/NCT01255904

Study 23:
Title: Placebo-Controlled Evaluation of Intranasal Dexmedetomidine for Postoperative Analgesia Following Bunionectomy
Recruitment: Terminated
Study Results: Has Results
Conditions: Pain, Post-operative
Interventions: Drug: Intranasal Dexmedetomidine|Other: Intranasal Placebo
URL: https://ClinicalTrials.gov/show/NCT02169336

Study 24:
Title: Study Using Dexmedetomidine to Decreases Emergence Delirium in Pediatric Patients

Recruitment: Unknown status
Study Results: No Results Available
Conditions: Otitis Media
Interventions: Drug: dexmedetomidine|Drug: saline
URL: https://ClinicalTrials.gov/show/NCT00778063

Study 25:
Title: Dexmedetomidine in Children for Magnetic Resonance Imaging (MRI) Sedation
Recruitment: Completed
Study Results: No Results Available
Conditions: Anesthesia
Interventions: Drug: Dexmedetomidine
URL: https://ClinicalTrials.gov/show/NCT02299232

Study 26:
Title: Pharmacological Characteristics of Intranasally Given Dexmedetomidine in Paediatric Patients
Recruitment: Not yet recruiting
Study Results: No Results Available
Conditions: Procedural Sedation
Interventions: Device: Dexmedetomidine
URL: https://ClinicalTrials.gov/show/NCT02955732

Study 27:
Title: Dexmedetomidine Versus Fentanyl Following Pressure Equalization Tube Placement
Recruitment: Completed
Study Results: Has Results
Conditions: Chronic Otitis Media
Interventions: Drug: Dexmedetomidine|Drug: Fentanyl|Drug: Midazolam
URL: https://ClinicalTrials.gov/show/NCT01188551

Study 28:
Title: ED50 and ED95 of Intranasal Dexmedetomidine in Pediatric Patients Undergoing Transthoracic Echocardiography Study
Recruitment: Recruiting
Study Results: No Results Available
Conditions: Patients for Transthoracic Echocardiography|Unknown Diagnosis
Interventions: Drug: intranasal dexmedetomidine
URL: https://ClinicalTrials.gov/show/NCT02780427

Study 29:

Title: Intranasal Dexmedetomidine VS Oral Chloral Hydrate for Rescue Sedation During Magnetic Resonance Imaging
Recruitment: Completed
Study Results: No Results Available
Conditions: Administration Related Reaction|Failed Moderate Sedation During Procedure|Chloral Hydrate Adverse Reaction
Interventions: Drug: chloral hydrate Group|Drug: low dose dexmedetomidine group|Drug: high dose dexmedetomidine group
URL: https://ClinicalTrials.gov/show/NCT02239445

Study 30:
Title: A Study to Assess the Analgesia and Sedation Using Intranasal Dexmedetomidine in Third Molar Surgery Under Local Anaesthesia
Recruitment: Completed
Study Results: No Results Available
Conditions: Pain|Sedation
Interventions: Drug: Intranasal dexmedetomidine|Drug: Placebo
URL: https://ClinicalTrials.gov/show/NCT01132794

Study 31:
Title: The Effect of Age on the Median Effective Dose (ED50) of Intranasal Dexmedetomidine for Rescue Sedation Following Failed Sedation With Oral Chloral Hydrate During Magnetic Resonance Imaging
Recruitment: Completed
Study Results: No Results Available
Conditions: Aged|Drug|Dose-Response Relationship
Interventions: Drug: intranasal dexmedetomidine
URL: https://ClinicalTrials.gov/show/NCT02253199

Australian New Zealand Clinical Trials Registry

4 Results

1.
The effects of ketamine on the quality of sedation of intranasal dexmedetomidine premedication in children undergoing elective tonsillectomy.
ACTRN12616001522404
Registered
20/11/2016

2.

Intranasal dexmedetomidine versus intranasal ketamine for prevention of emergence agitation after sevoflurane anesthesia in pediatric patients undergoing myringotomy : a randomized clinical trial.
ACTRN12616000921482
Registered

3.
The Effect of Intranasal Dexmedetomidine Premedication on the Minimum Alveolar Concentration of Sevoflurane for tracheal intubation in children
ACTRN12613000679785
Registered
28/06/2013

4.
The Effect of Intranasal Dexmedetomidine Premedication on Reducing the Minimum Alveolar Concentration of Sevoflurane for the Insertion of Laryngeal Mask Airway in Children
ACTRN12613000462785
Registered
25/04/2013

EU Clinical Trials Register
8 Results

EudraCT Number: 2016-002880-33
Sponsor Protocol Number: PINDEX
Sponsor Name: University of Turku
Full Title: Bioavailability and pharmacokinetics of intranasal dexmedetomidine in children
Start Date: 2016-10-28
Medical condition: Paediatric patients scheduled for minor procedures such as intra-articular drug injections, hernia repair, bronchoscopy or magnetic resonance imaging.
Disease:
Population Age: Children, Under 18
Gender: Male, Female
Trial protocol: FI(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-002880-33

EudraCT Number: 2016-002065-66
Sponsor Protocol Number: OY102016
Sponsor Name: Miikka Tervonen
Full Title: Intranasal dexmedetomidine sedation during intra-articular joint injections in pediatric population

Start Date: 2016-11-07
Medical condition: All the patients from 1year to 18 years of age who have been diagnosed by a pediatric rheumatologist to have a joint inflammation needing intra-articular corticosteroid injection in 1 to 5 joints
Disease:
Population Age: Infants and toddlers, Children, Adolescents, Under 18, Adults
Gender: Male, Female
Trial protocol: FI(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-002065-66

EudraCT Number: 2016-001567-37
Sponsor Protocol Number: KUKIDEX-2
Sponsor Name: University Medical Center Groningen
Full Title: Efficacy of single dose intranasal dexmedetomidine for conscious sedation in dental practice in dentophobic uncooperative patients with intellectual disability.
Start Date: 2016-11-24
Medical condition: dentophobia
intellectual disability
Disease:
Population Age: Adults
Gender: Male, Female
Trial protocol: NL(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-001567-37

EudraCT Number: 2008-008324-33
Sponsor Protocol Number: 900, version 1.0
Sponsor Name: Sanna Vilo
Full Title: Bioavailability of dexmedetomidine after intranasal administration in healthy subjects
Start Date: 2009-03-18
Medical condition: healthy volunteers
Disease:
Population Age: Adults, Elderly
Gender: Male
Trial protocol: FI(Completed)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-008324-33

EudraCT Number: 2015-004587-11
Sponsor Protocol Number: KUKIDEX-1
Sponsor Name: University Medical Center Groningen

Full Title: Safety, tolerability and sedative properties of single dose intranasal dexmedetomidine premedication in elderly subjects.
Start Date: 2016-01-08
Medical condition: Anxiety, preoperative
Disease:
Population Age: Elderly
Gender: Male, Female
Trial protocol: NL(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-004587-11

EudraCT Number: 2017-000057-40
Sponsor Protocol Number: dex_vs_ket
Sponsor Name: Karolinska University Hospital
Full Title: A prospective randomized double-blind study Intranasal dexmedetomidine versus intranasal S-ketamine for children age 1 – 3 years for procedural sedation and analgesi pediatric emergency departm...
Start Date: 2017-06-12
Medical condition: sedation for emergency procedures
Disease:
Population Age: Infants and toddlers, Children, Under 18
Gender: Male, Female
Trial protocol: SE(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-000057-40

EudraCT Number: 2016-003773-17
Sponsor Protocol Number: dex_version1
Sponsor Name: Karolinska University Hospital
Full Title: A prospective randomized open label study Intranasal dexmedetomidine versus inhaled nitrous oxide for children age 3 – 15 years for procedural sedation and analgesi in pediatric emergency departme...
Start Date: 2017-06-12
Medical condition: sedation for emergency procedures
Disease:
Population Age: Children, Adolescents, Under 18
Gender: Male, Female
Trial protocol: SE(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-003773-17

EudraCT Number: 2015-002102-37

Sponsor Name: Fundació Parc Taulí
Full Title: Open randomized clinical trial to compare the efficacy of hypotensive anesthesia with clonidine or dexmedetomidine during endoscopic nasal surgery
Start Date: 2015-10-02
Medical condition: Nasosinusal endoscopic surgery in patients with chronic sinusitis and/or nasal polyposis
Disease: Version: 18.0, SOC Term: 10021881 - Infections and infestations, Classification Code: 10009137, Term: Chronic sinusitis, Level: PT
Disease: Version: 18.0, SOC Term: 10042613 - Surgical and medical procedures, Classification Code: 10028755, Term: Nasal polypectomy, Level: PT
Population Age: Adults
Gender: Male, Female
Trial protocol: ES(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-002102-37

WHO ICTRP
22 Results

Recruitment status	Prospective Registration	Main ID	Public Title	Date of Registration
Authorised	**Yes**	**EUCTR2016-003773-17-SE**	**Comparison of intranasally given drug dexmedetomidine with N2O (=laughing gas) for sedation for small procedures in children's emergency department.**	**13/01/2017**
Authorised	Yes	EUCTR2017-000057-40-SE	Comparison of intranasally given drug dexmedetomidine with intranasal S-keramine for sedation for small procedures in children's emergency department.	13/01/2017
Recruiting	Yes	ChiCTR-IIR-16010263	Comparison of Rapid IV Bolus and Intranasal Adminstration of Dexmedetomidine for Treatment and	2016-12-27

			Prophylaxis of Emergence Agitation in Anesthetized Pediatric Patient	
Recruiting	Yes	NCT03069638	Intranasal Dexmedetomidine Sedation During Intra-articular Joint Injections in Pediatric Population	20/12/2016
Recruiting	Yes	ChiCTR-OOC-16009846	Median Effective Dose of intranasal dexmedetomidine sedation for Pediatric transthoracic echocardiography between the children with and without history of cardiac operation: A Biased-Coin Up-and-Down Sequential Allocation Trial	2016-11-13
Recruiting	Yes	ChiCTR-OPC-16009842	Efficacy study of intranasal dexmedetomidine for pediatric sedation	2016-11-13
Recruiting	Yes	ChiCTR-IOR-16009780	Effects of intranasal dexmedetomidine combined with ketamine sedation for echocardiography in pediatric patients with congenitial heart disease	2016-11-08
Authorised	Yes	EUCTR2016-002065-66-FI	Intranasal dexmedetomidine sedation during intra-articular joint injections in pediatric population	02/11/2016

Authorised	Yes	EUCTR2016-002880-33-FI	Pharmacological characteristics of intranasally given dexmedetomidine in paediatric patients	17/10/2016
Authorised	Yes	EUCTR2016-001567-37-NL	Efficacy of dexmedetomidine for conscious sedation during dental treatement of uncooperative patients with intellectual disability and fear of dentists.	20/07/2016
Recruiting	Yes	NCT02780427	ED50 and ED95 of Intranasal Dexmedetomidine in Pediatric Patients Undergoing Transthoracic Echocardiography Study	12/05/2016
Recruiting	Yes	IRCT201601281882N7	Premedication effect of intranasal midazolam and dexmedetomidine on children behavior	2016-03-13
Recruiting	Yes	ChiCTR-IOR-16008076	Evaluation of Efficacy and Safety of Intranasal Dexmedetomidine Premedication for Hypertension Patients	2016-03-09
Recruiting	Yes	NCT02836431	Pharmacokinetic Study of Dexmedetomidine After Intra-nasal Dosing in Children	08/01/2016
Authorised	Yes	EUCTR2015-004587-11-NL	Is dexmedetomidine a safe medicine to calm elderly patients when they are waiting for an operation?	17/12/2015

Recruiting	Yes	NCT02459509	A Comparison of Two Doses of Intranasal Dexmedetomidine for Premedication in Children	20/05/2015
Recruiting	Yes	ChiCTR-TRC-14004886	A randomized, double-blind assessment of the sedative and analgesic effects of intranasal dexmedetomidine in nasal endoscopic surgery cases	2014-07-02
Recruiting	Yes	NCT02108171	Intranasal Dexmedetomidine Premedication	30/03/2014
Recruiting	Yes	NCT02077712	Intranasal Dexmedetomidine Sedation for Ophthalmic Examinations in Children	27/02/2014
Recruiting	Yes	NCT01900405	Intranasal Dexmedetomidine Sedation for Pediatric CT Imaging	09/07/2013
Recruiting	No	NCT01065701	Comparison of Two Doses of Intranasal Dexmedetomidine as Premedication in Children	07/02/2010
Recruiting	Yes	NCT00778063	Study Using Dexmedetomidine to Decreases Emergence Delirium in Pediatric Patients	21/10/2008

Conference Abstracts

Association of Anaesthetists of Great Britain and Ireland Annual Congress (2012-2016)
American Society for Pediatric Anesthesia Annual Meeting (2013-2016)
Canadian Anesthesiologists' Society Annual Meeting (2012-2015)
The Congress of the European Pain Federation (2013-2015)

European Society of Intensive Care Medicine (2012-2016)
European Society of Anaesthesiology (2012-2016)
European Society of Regional Anaesthesia (2012-2016)
Canadian Association of Emergency Physicians (2012-2017)
Society of Academic Emergency Medicine (2012-2016)
Australasian College for Emergency Medicine (2012-2016)
International Federation on Emergency Medicine (2012)
European Society of Emergency Medicine (2013-2016)
Canadian Paediatric Society (2014-2016)

List word counts below (do not paste the text here). Please see the Decision Letter Attachment for allowances as they pertain to your manuscript type.

# of words in Abstract: 250 (250 words allowed)
# of words in Manuscript Body: 3685 (3000 allowed for Regular Articles/Quality Reports; 4000 Reviews/Special Articles; 800 Commentaries; 1200 Perspectives)
# of characters in Main Title: 83 characters (97 characters allowed, including spaces)
# of characters in Short Title: 50 (55 characters allowed, including spaces)
# of words in "Table of Contents Summary": 19 (25 words allowed; this section appears in all articles with abstracts)
# of words in "What's Known on this Subject": 40 (40 words allowed; this section appears in Regular Articles only)
# of words in "What this Study Adds": 40 (40 words allowed; this section appears in Regular Articles only)

2019-1623.R2 – Intranasal dexmedetomidine for procedural distress in children: a systematic review -- by Poonai et al.

Editor/Reviewer Comments *Paste each of the editor and reviewer queries here.*	**Author's Response** *Paste your answer to the editor and reviewer queries here. If you alter your manuscript to address this query, you MUST paste the relevant altered text here – verbatim as it appears in the manuscript.*	**Reference Page** *State where* the change now appears in your newly revised manuscript.*	**Change Approved? FOR EDITORIAL USE ONLY**
EXAMPLE: Reviewer 1's comment	EXAMPLE: A brief response to this reviewer's comment. The text now states: "insert relevant changed text here"	EXAMPLE 1: Page 7, lines 10-22 EXAMPLE 2: No change	
Please consider rewriting the abstract results to make it a bit less confusing	Thank you. The following changes to the abstract results have been made with respect to wording. The terms "favorable", "neutral", and "unfavorable" were replaced with "superior", "equivalent", and "inferior" to improve readability and general comprehension.	Abstract	
Change the short title (both in your paper and in online Step 1) to: Intranasal dexmedetomidine for procedural distress	The short title has been changed.	Title	
The sedation instruments used by various studies has been removed from the current version. It was there is the initial submission. I am wondering if there a specific reason the authors removed it from the revised version. If there is no reason it may be better to add it back.	We initially removed this part of the text to reduce the word count. We have added this back in as per your recommendation. A validated sedation instrument was used in ten trials (25-27, 29-34, 36) and included the Observer's Assessment of Alertness/Sedation, Modified Observer's Assessment of Alertness/Sedation Scale, Ramsay Sedation Scale, and the University of Michigan Sedation Scale (Table 1).	Page 9, lines 256-259	

Line 262: The authors may have inadvertently omitted "participants"—"The proportion with adequate sedation was 33/41 (80.4%) participants (?). " Otherwise it is a little confusing as to what it means. It is present in the rest of the manuscript.	We have made this correction. The proportion of participants with adequate sedation was 33/41 (80.4%) for IND plus oral ketamine…	Page 9-10, lines 263-264	
The authors have reported the overall adverse events. Would they be able to comment if the adverse events- particularly bradycardia and hypo/hypertension was greater with IND (or similar). I think it was reported in the initial submission.	Thank you for this comment. The revised (last submitted) version reports adverse events per interventions which are groups as follows: IND, IND + another sedation, and non-IND comparator. Bradycardia and hypotension are listed first. Inferential statistics were not performed because the meta-analysis was deconstructed for all outcomes including adverse events. The section reads: Across the remaining 18 trials, the most common adverse events of IND, IND plus another sedative, or non-IND comparator were bradycardia [32/1484 (2.2%), 0/41 (0%), and 6/595 (1%), respectively], hypotension [18/1484 (1.2%), 0/41(0%), and 9/595 (1.5%), respectively], oxygen desaturation [7/1484 (0.5%), 0/41 (0%), and 12/595 (2%), respectively], and vomiting [6/1484 (0.4%), 3/41 (7.3%), and 47/595 (7.9%), respectively].	Page 12, lines 322-327	
2nd para: The NICE guidelines are from 2010. Chloral hydrate is no longer available in the United States. https://medlineplus.gov/druginfo/meds/a682201.html I think it is completely acceptable that this review looked at chloral hydrate as one of the comparators. It may still be used in other countries. However, it is important that the above information that it is not approved by the FDA should be included - since this article will be reaching pediatricians in the US as well.	This is a very important point and we thank you for raising it. The section has been revised to read: In fact, chloral hydrate is recommended by the National Institute for Health and Care Excellence (NICE) 2010 guideline for moderate sedation for painless procedures in children (44). While chloral hydrate is no longer approved by the United States Food and Drug Administration, it may still be used in other countries.	Page 13-14, lines 354-355	

Instructions:

Please use this table format to answer the questions posed by the editors and reviewers of your paper. Copy and paste the editor/reviewer's question in the "Comments" column and your answer to that question in the corresponding "Response" column. Be sure to ALSO paste the corrected text along with your response. For minor copyediting changes such as spelling and grammar corrections, you may simply state that the error was corrected, without pasting the altered text.
* Use the page/line numbers from your revised .doc, .rtf, or .txt file; do *not* use the page/line numbers from the submission system's auto-generated PDF.

For clarity, use one row per question. Make sure to list the page and line reference where your change can be found. If no change was made, please make sure to note that in your response in addition to your reasoning. You may delete the sample row and insert rows to this table as needed.

Appendix B Pediatric Sedation State Scale (PSSS)

TABLE 2 PSSS

State	Behavior
5	Patient is moving (purposefully or nonpurposefully) in a manner that impedes the proceduralist and requires forceful immobilization. This includes crying or shouting during the procedure, but vocalization is not required. Score is based on movement.
4	Moving during the procedure (awake or sedated) that requires gentle immobilization for positioning. May verbalize some discomfort or stress, but there is no crying or shouting that expresses stress or objection.
3	Expression of pain or anxiety on face (may verbalize discomfort), but not moving or impeding completion of the procedure. May require help positioning (as with a lumbar puncture) but does not require restraint to stop movement during the procedure.
2	Quiet (asleep or awake), not moving during procedure, and no frown (or brow furrow) indicating pain or anxiety. No verbalization of any complaint.
1	Deeply asleep with normal vital signs, but requiring airway intervention and/or assistance (eg, central or obstructive apnea, etc).
0	Sedation associated with abnormal physiologic parameters that require acute intervention (ie, oxygen saturation <90%, blood pressure is 30% lower than baseline, bradycardia receiving therapy).

Appendix C

The Council for International Organizations of Medical Sciences (CIOMS)

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP	

Appendix D

<u>Post-Hospital Behavior Questionnaire (PHBQ)- Follow up between 24 to 48 hours after discharge</u> (Hilly J, 2015)

1. Does your child make a fuss about going to bed at night?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

2. Does your child make a fuss about eating?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

3. Does your child spend time just sitting or lying and doing nothing?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

4. Does your child need a pacifier?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

5. Does your child seem to be afraid of leaving the house with you?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

6. Is your child uninterested in what goes on around him (or her)?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

7. Does your child wet the bed at night?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

8. Does your child bite his (or her) finger nails?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

9. Does your child get upset when you leave him (or her) alone for a few minutes?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

10. Does your child need a lot of help doing things?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

11. Is it difficult to get your child interested in doing things (like playing games with toys/ video games)?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

12. Does your child seem to avoid or be afraid of new things?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

13. Does your child have difficulty making up his (or her) mind?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

14. Does your child have temper tantrums?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

15. Is it difficult to get your child to talk to you?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

16. Does your child seem to get upset when someone mentions doctors or hospitals?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

17. Does your child follow you everywhere around the house?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

18. Does your child spend time trying to get or hold your attention?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

19. Is your child afraid of the dark?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

20. Does your child have bad dreams at night or wake up and cry?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

21. Does your child have irregular bowel movements?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

22. Does your child have trouble getting to sleep at night?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

23. Does your child seem to be shy around strangers?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

24. Does your child have a poor appetite?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

25. Does your child tend to disobey you?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

26. Does your child break toys or other objects?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

27. Does your child suck his (or her) fingers or thumbs?

Much less than before (1) Less than before (2) Same as before (3) More than before (4) Much more than before (5)

Appendix E

PRODUCT MONOGRAPH

PRECEDEX®

Dexmedetomidine Hydrochloride for Injection
100 mcg/mL dexmedetomidine (as dexmedetomidine hydrochloride)
(Concentrate, 2 mL vial)

Dexmedetomidine Hydrochloride Injection
4 mcg/mL dexmedetomidine (as dexmedetomidine hydrochloride)
(Ready to use, 20 mL, 50 mL and 100 mL vials)

Alpha$_2$-adrenergic agonist

Pfizer Canada Inc.
17300 Trans-Canada Highway
Kirkland, Québec
H9J 2M5

Date of Revision:
March 6, 2018

Submission Control No.: 213361

Table of Contents

PRECEDEX®

Dexmedetomidine Hydrochloride for Injection
Dexmedetomidine Hydrochloride Injection

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Intravenous infusion	Parenteral injection,100 mcg/mL in a 2 mL vial (Concentrate)	Sodium Chloride and Water for Injection
	Parenteral injection,4 mcg/mL in 20 mL, 50 mL and 100 mL vials (Ready to Use)	

INDICATIONS AND CLINICAL USE

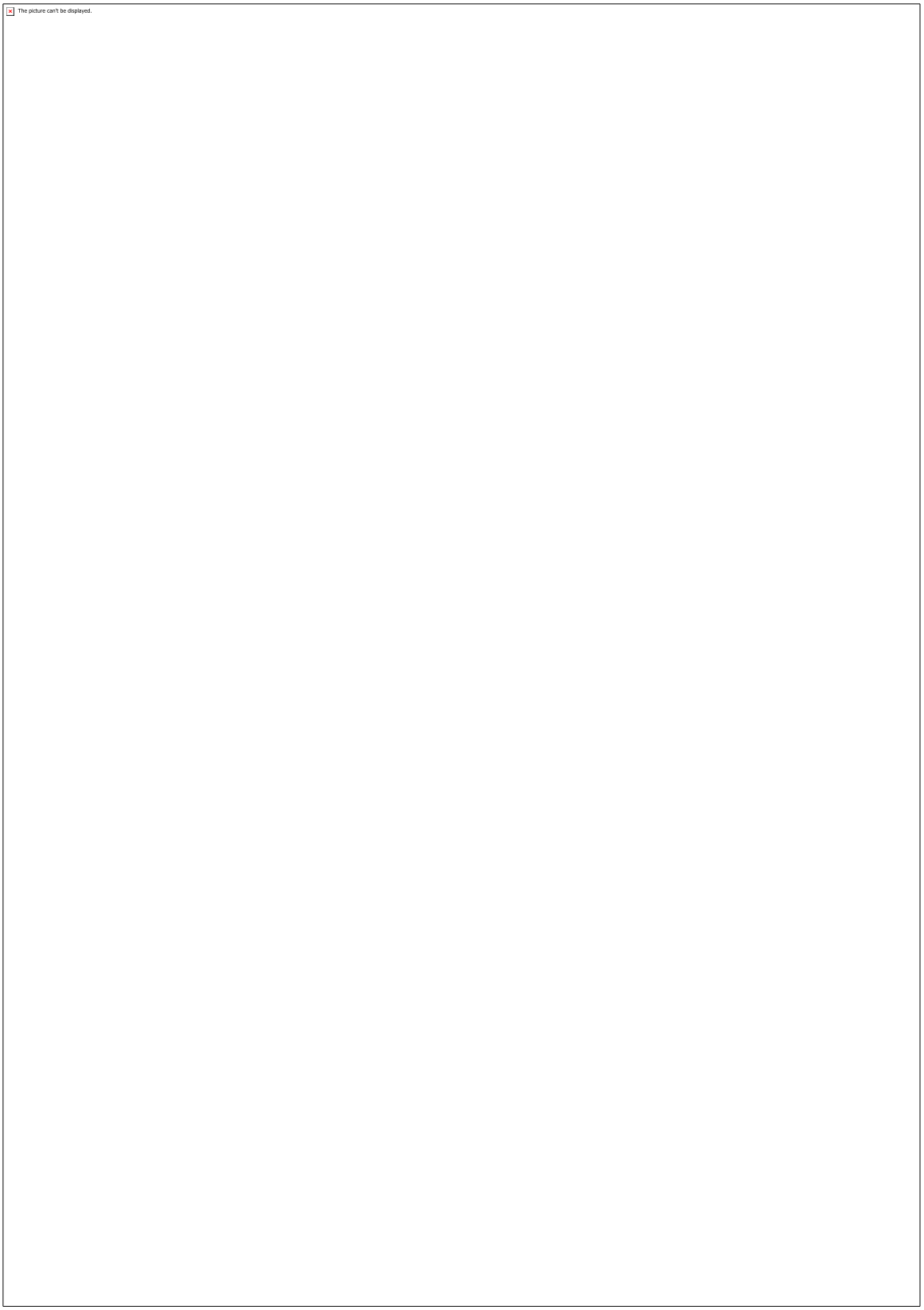
Precedex® (Dexmedetomidine Hydrochloride for Injection and Dexmedetomidine Injection) is indicated for:

- **Intensive Care Unit Sedation**
  Precedex® is indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive care setting by continuous intravenous infusion. The Precedex® infusion should not generally exceed 24 hours.

  Precedex® has been continuously infused in mechanically ventilated patients prior to extubation, during extubation, and post-extubation. It is not necessary to discontinue Precedex® prior to extubation.

- **Conscious Sedation**
  Precedex® is indicated for sedation of non-intubated patients prior to and/or during surgical and other procedures by continuous intravenous infusion for the following procedures:
  - Monitored Anesthesia Care (MAC) with an adequate nerve block and/or local infiltration; and
  - Awake Fiberoptic Intubation (AFI) with adequate topical preparation of the upper airway with local lidocaine formulations.

  Due to insufficient safety and efficacy data, Precedex® is not recommended for use in procedures other than the two listed above.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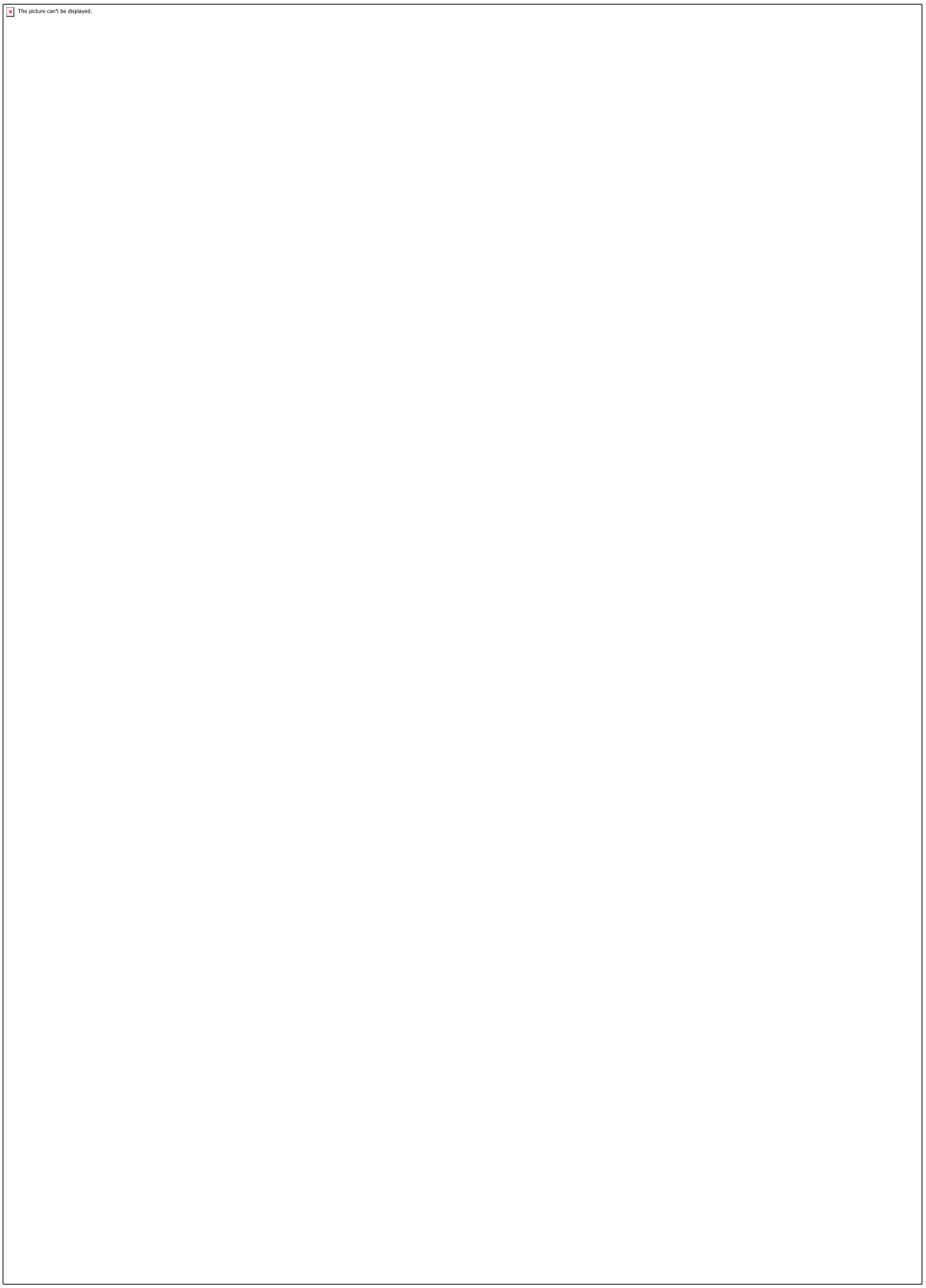
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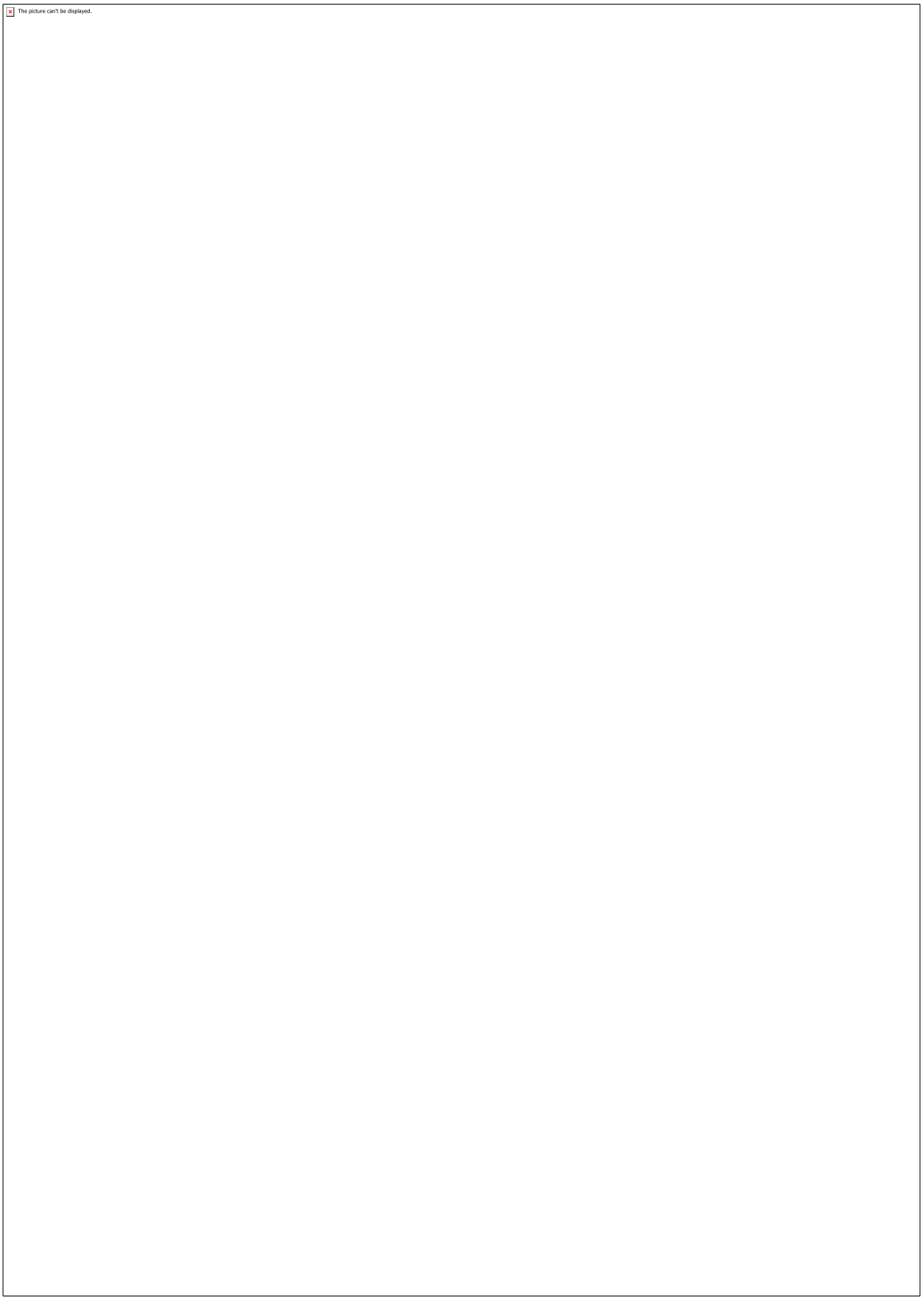
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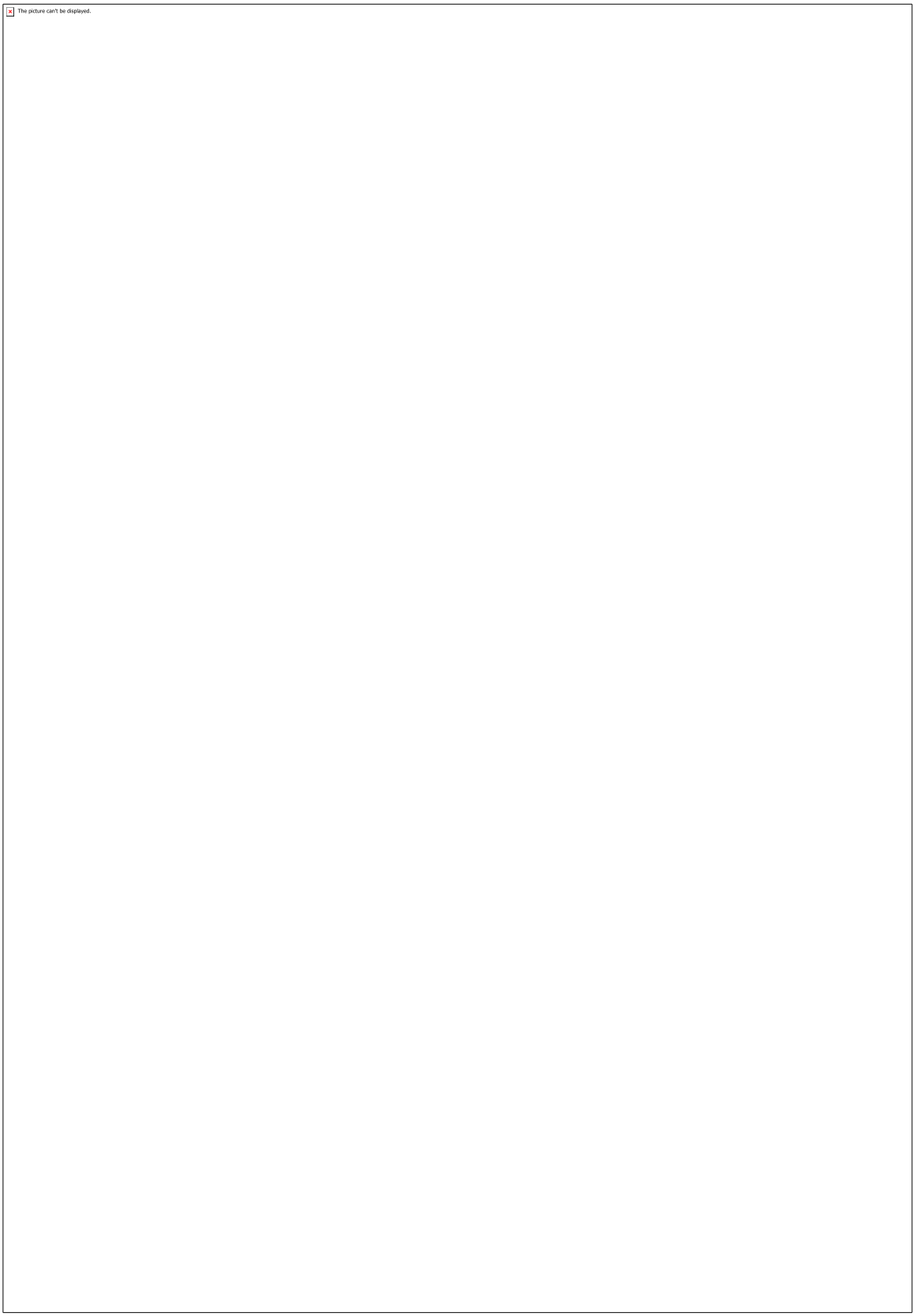
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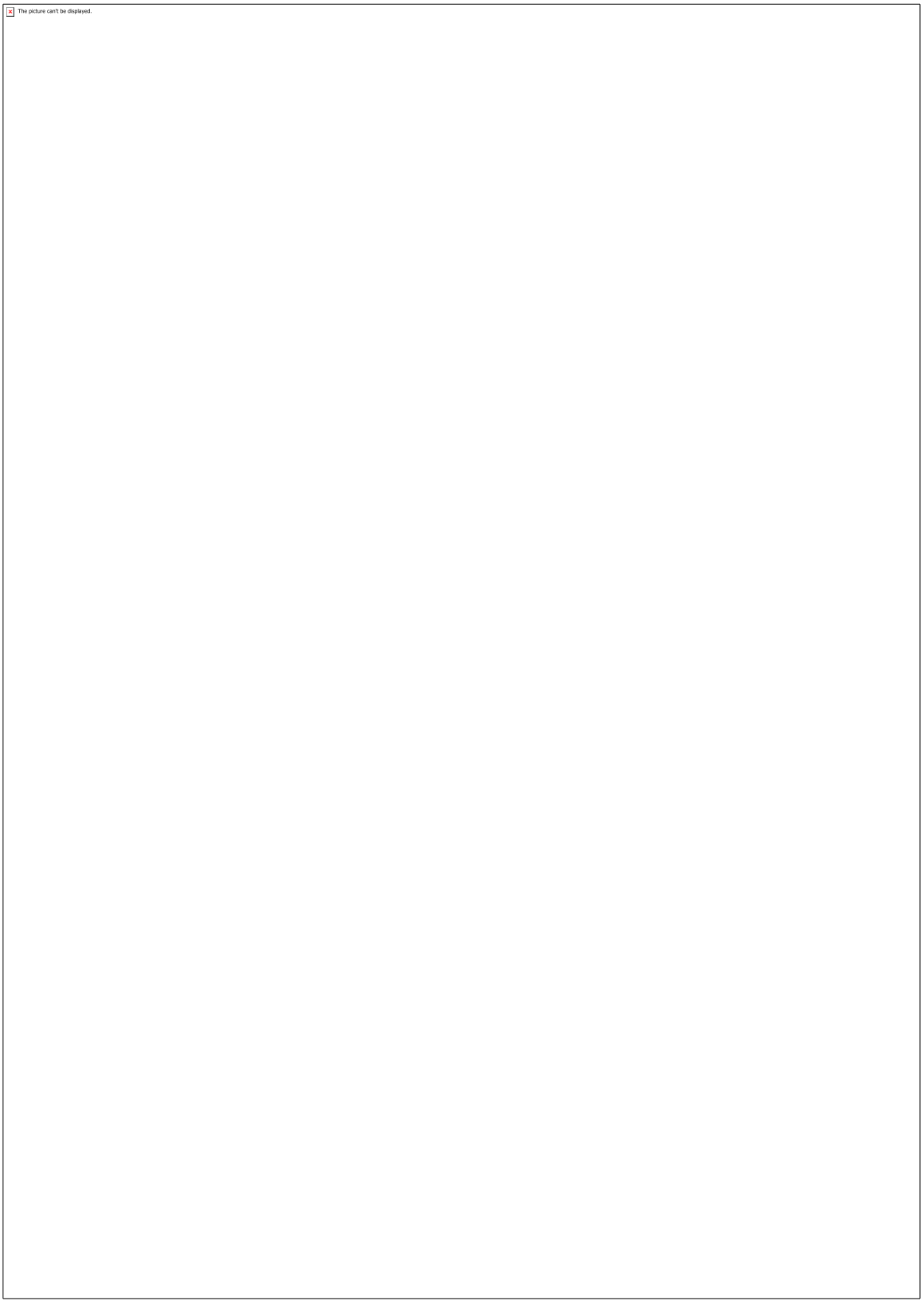
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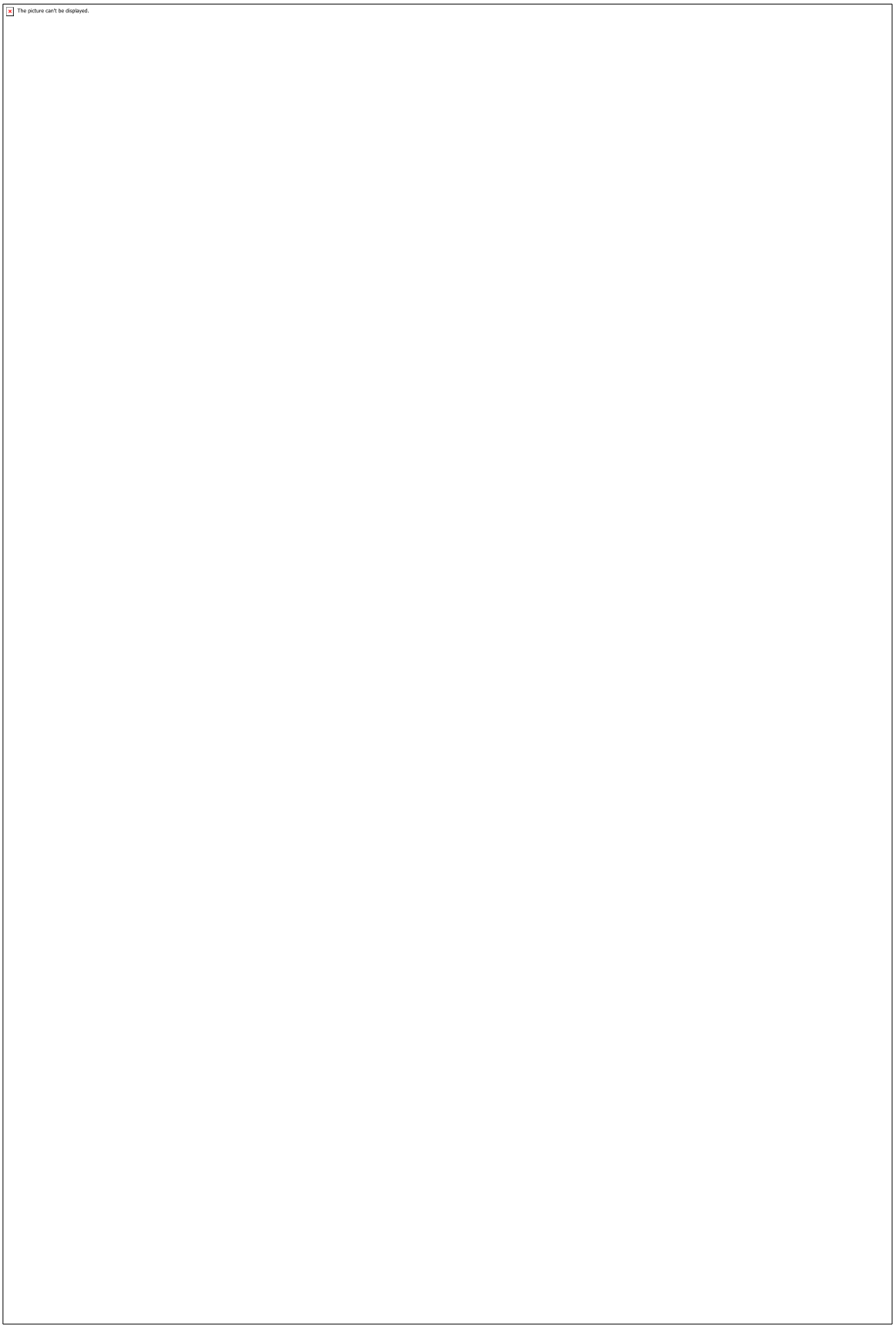
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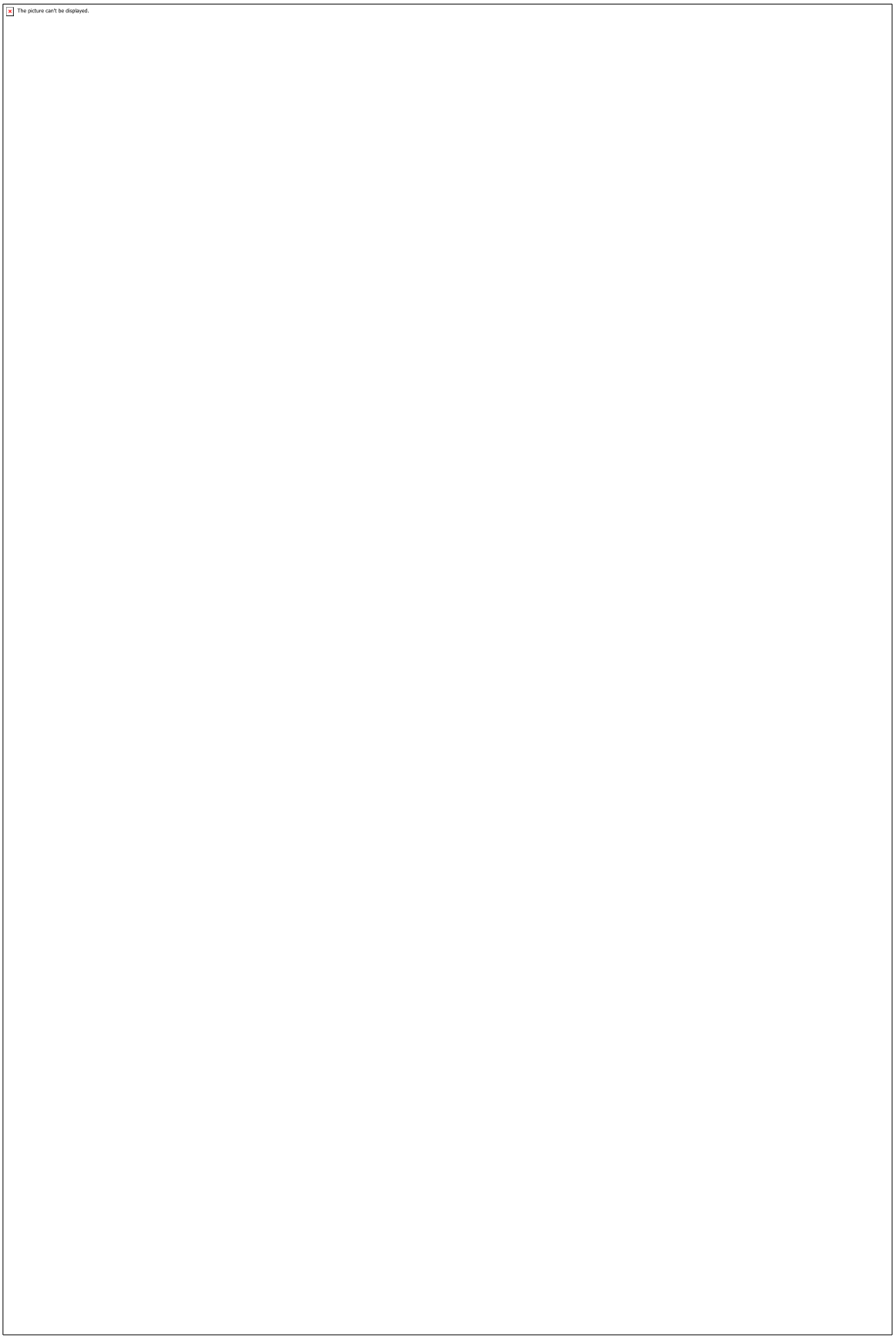
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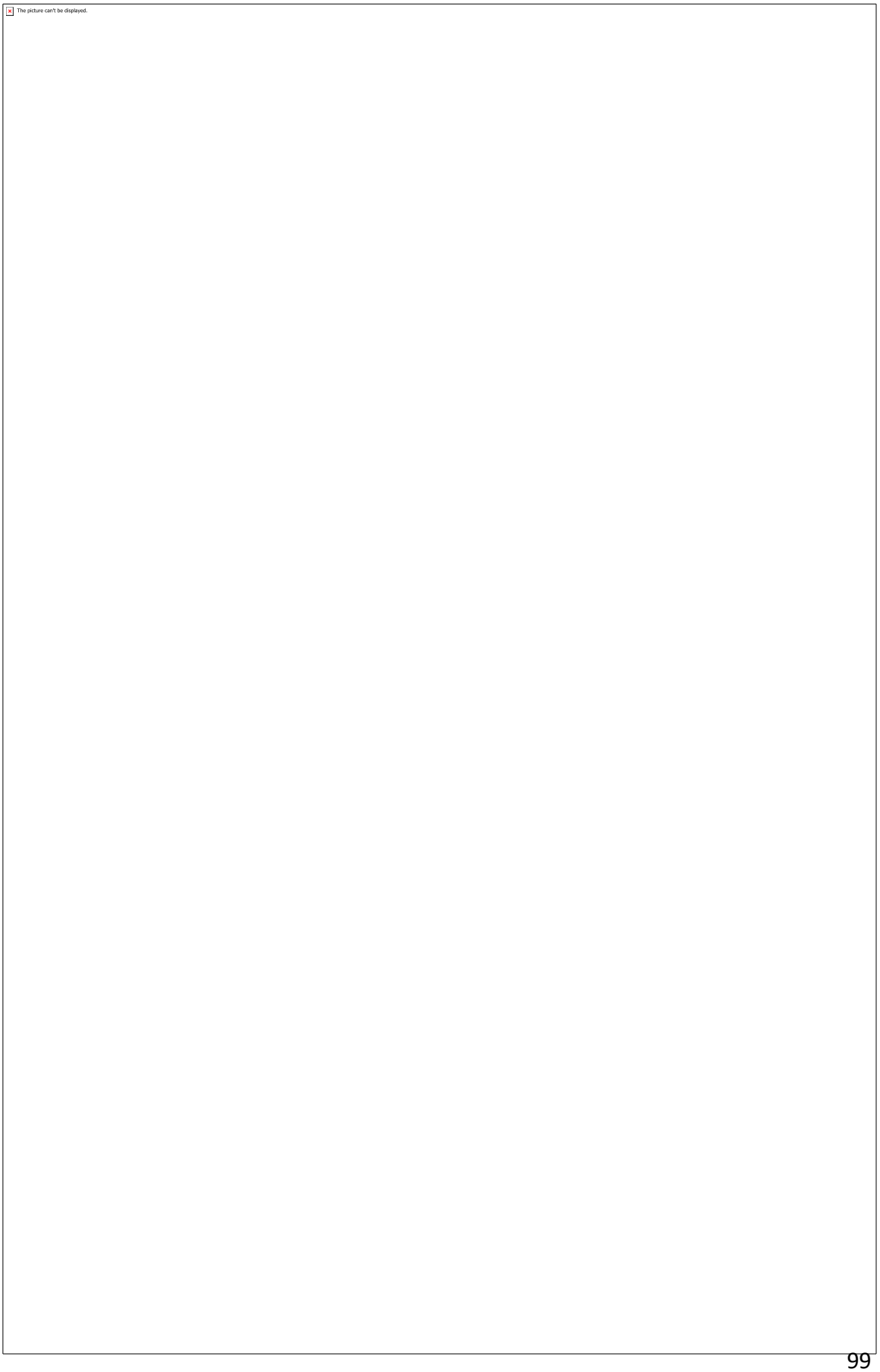
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Respiratory System Disorders	Apnea, bronchospasm, dyspnea, hypercapnia, hypoventilation, hypoxia, pulmonary congestion
Skin and Appendages Disorders	Increased sweating
Vascular disorders	Hemorrhage
Vision Disorders	Photopsia, abnormal vision

DRUG INTERACTIONS

Drug-Drug Interactions

Anesthetics, sedatives, hypnotics, opioids
Co-administration of Precedex® with anesthetics, sedatives, hypnotics, and opioids is likely to lead to an enhancement of effects. Specific studies have confirmed enhanced effects with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. No pharmacokinetic interactions between Precedex® and isoflurane, propofol, alfentanil and midazolam have been demonstrated. However, due to possible pharmacodynamic interactions, when co-administered with Precedex®, a reduction in dosage of Precedex® or the concomitant anesthetic, sedative, hypnotic or opioid may be required.

Neuromuscular Blockers
In one study of 10 healthy adult volunteers, administration of Precedex® for 45 minutes at a plasma concentration of 1 (one) ng/mL resulted in no clinically meaningful increases in the magnitude of neuromuscular blockade associated with rocuronium administration.

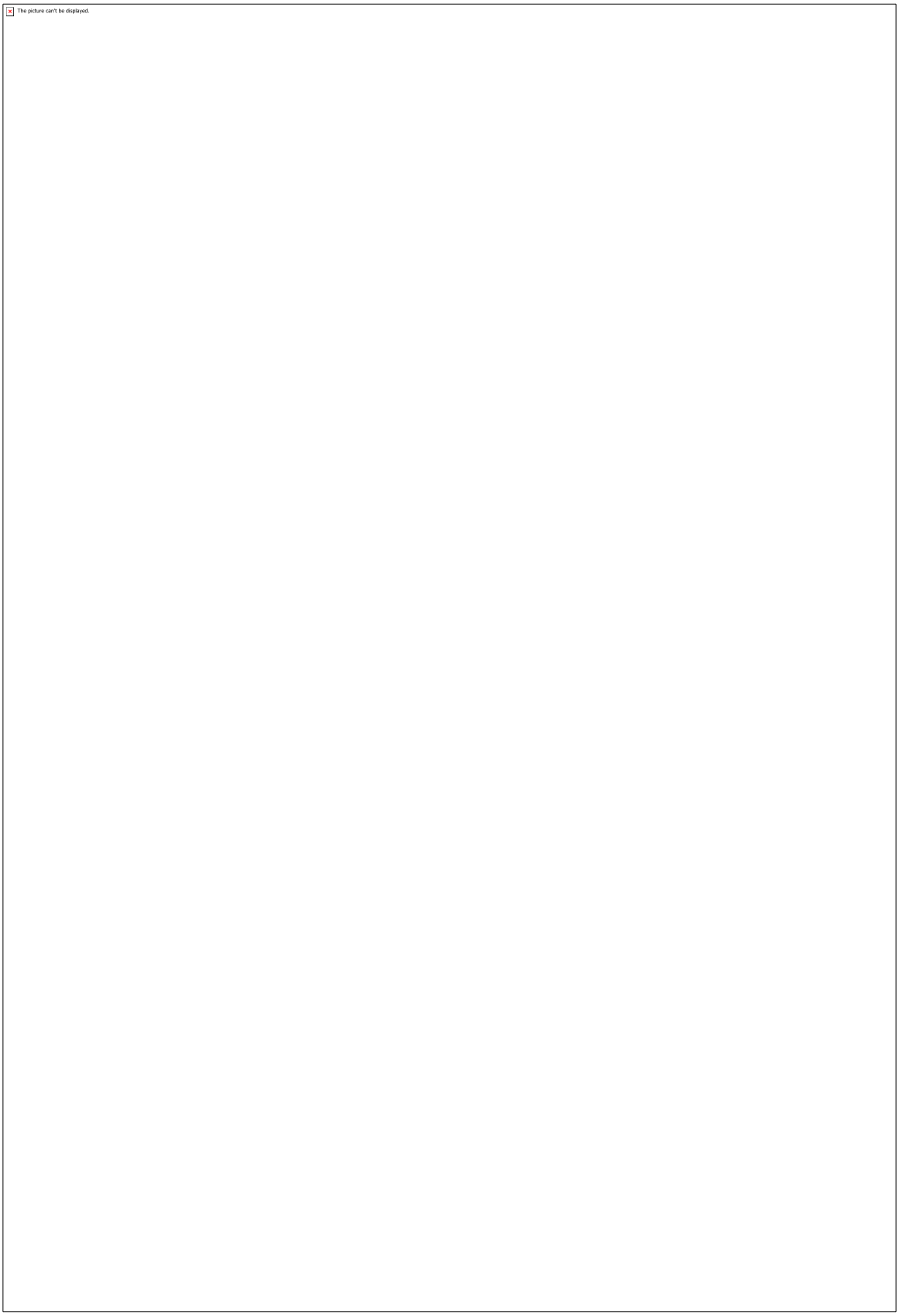
Drugs with cardiovascular activities
Precedex® is known to be associated with hypotension and bradycardia, especially during its initial use. However, it may also be associated with a transient or paradoxical hypertension which may occur during the initial use and maintenance use. Concomitant medications acting on the cardiovascular system should be reviewed, in addition to reducing the dexmedetomidine dose and/or using a vasodilator.

Cytochrome P-450
In vitro studies in human liver microsomes demonstrated no evidence of cytochrome P450 mediated drug interactions that are likely to be of clinical relevance.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Precedex® should be used only in facilities adequately staffed and equipped for anesthesia, resuscitation, and cardiovascular monitoring.
- Precedex® should not be generally used for duration longer than 24 hours. Its continued use beyond 24 hours should be determined based on careful assessment of the patient's conditions.
- Precedex® should be administered using a controlled infusion device with adequate precision.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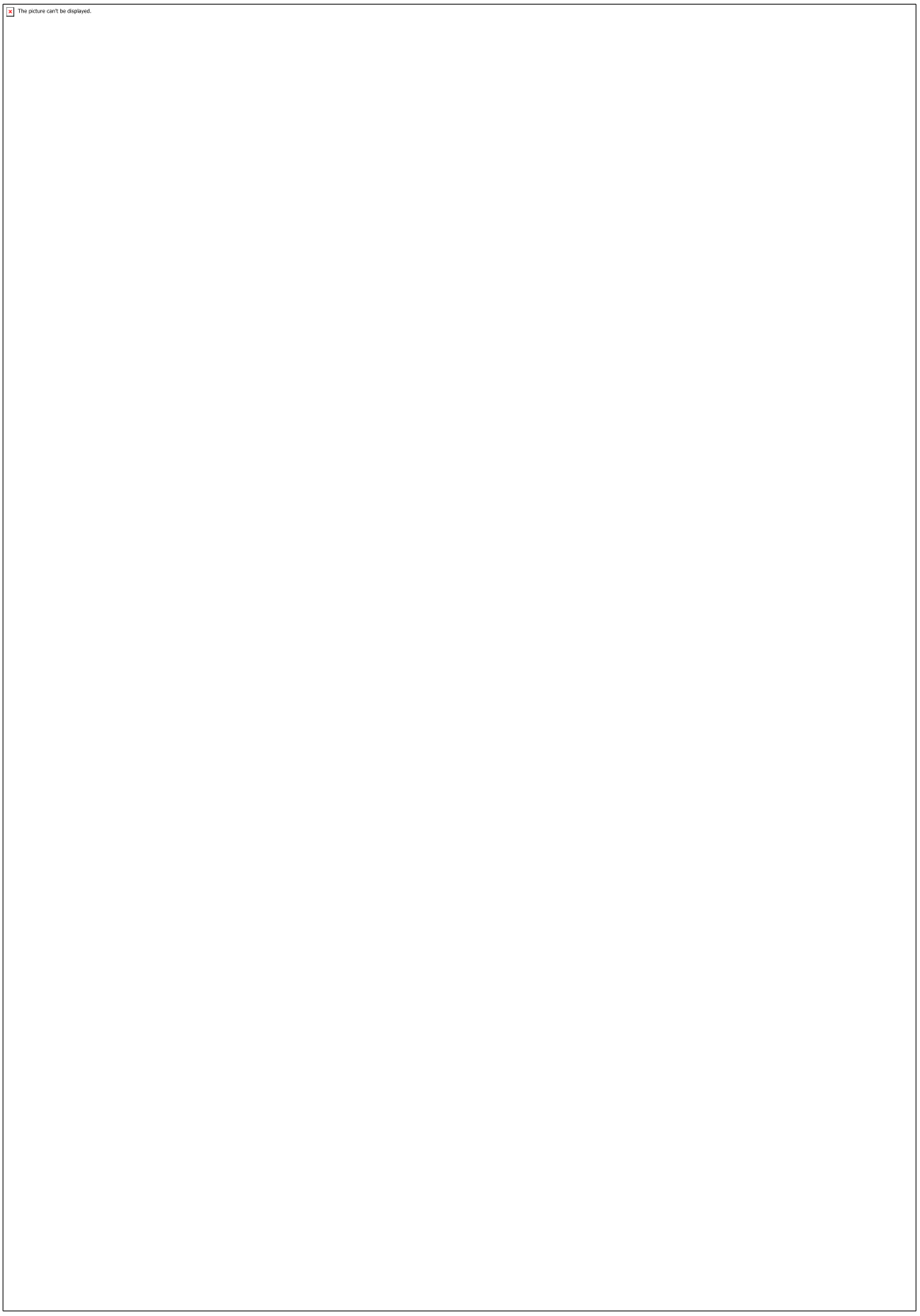
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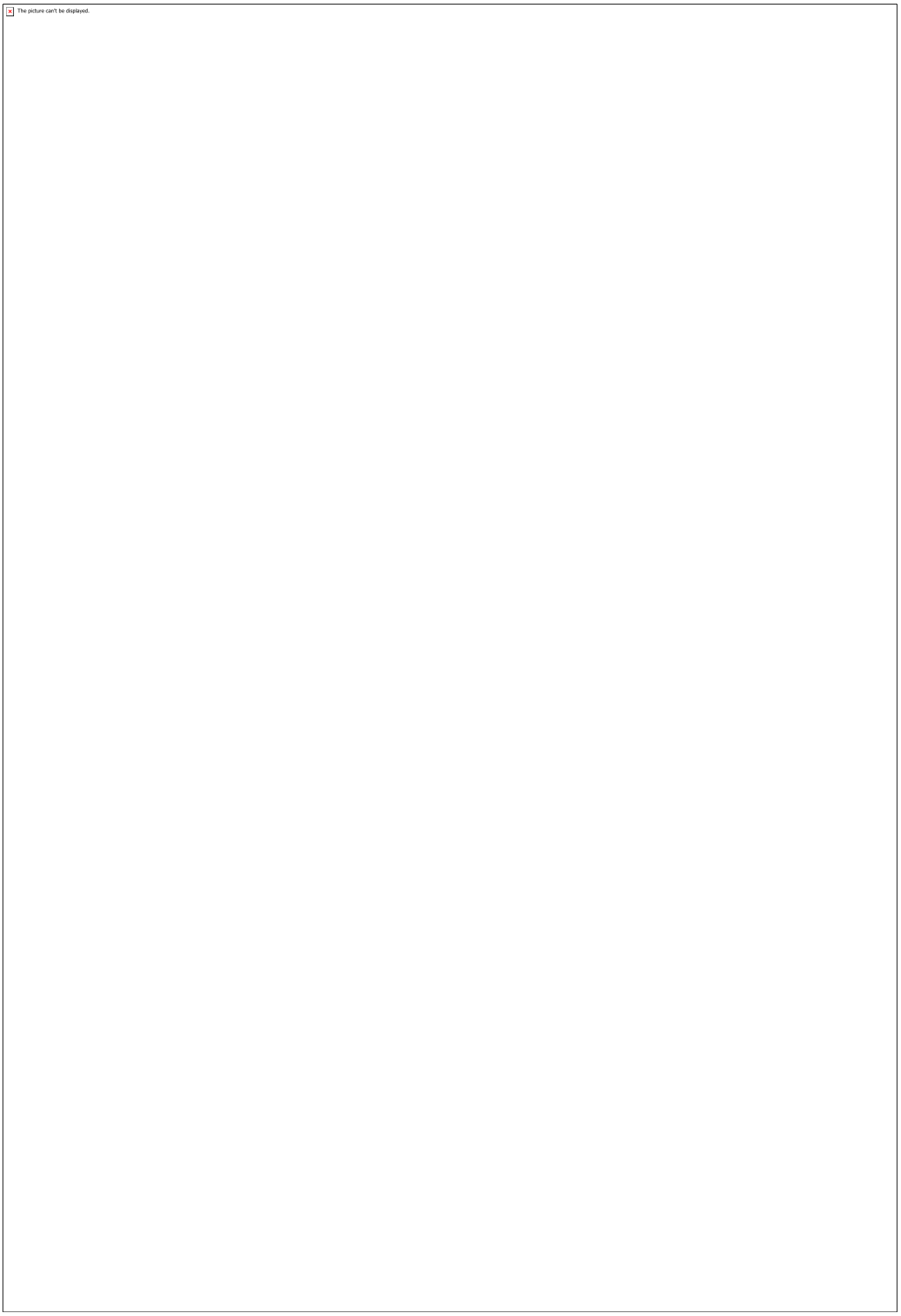
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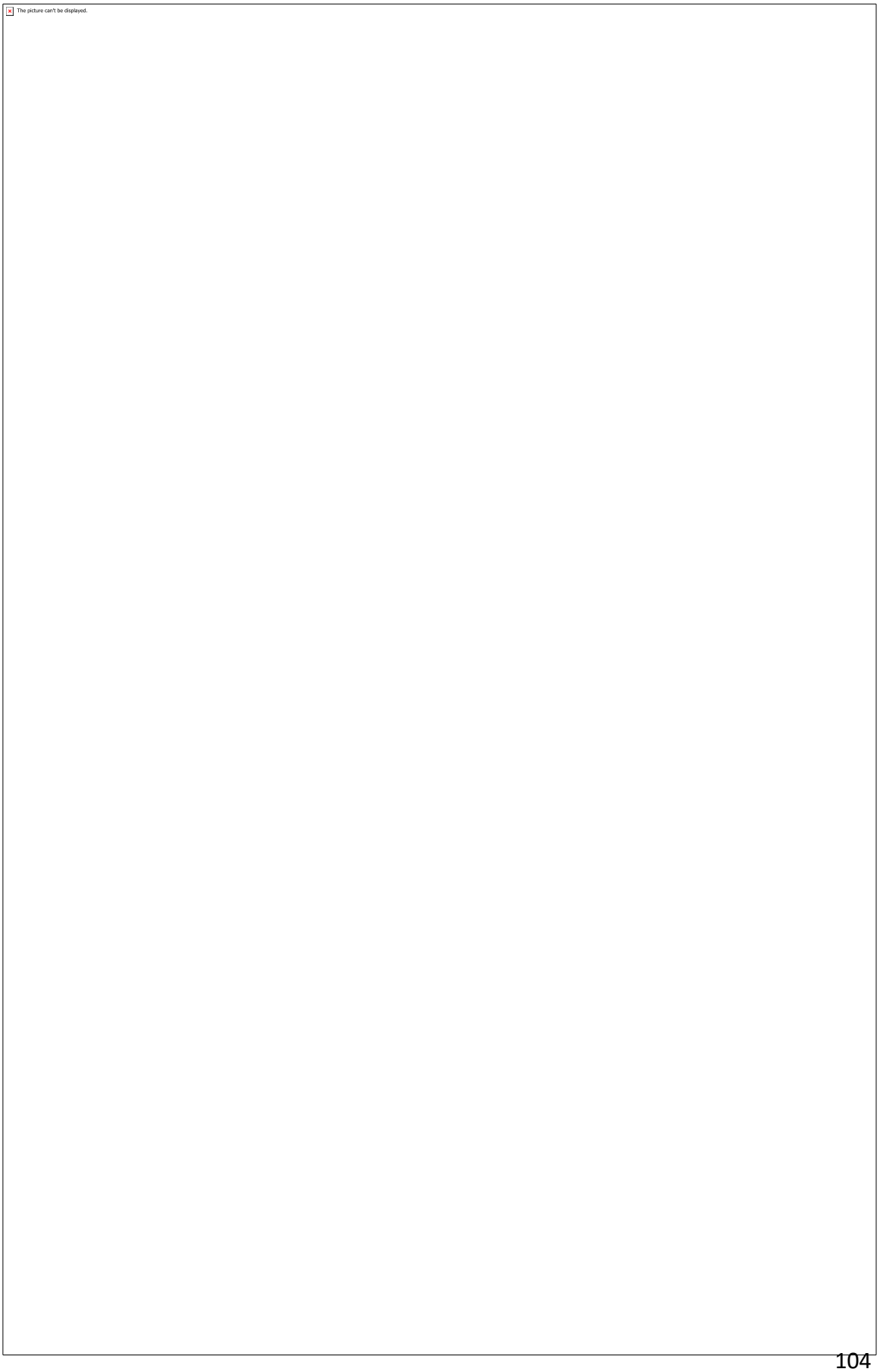
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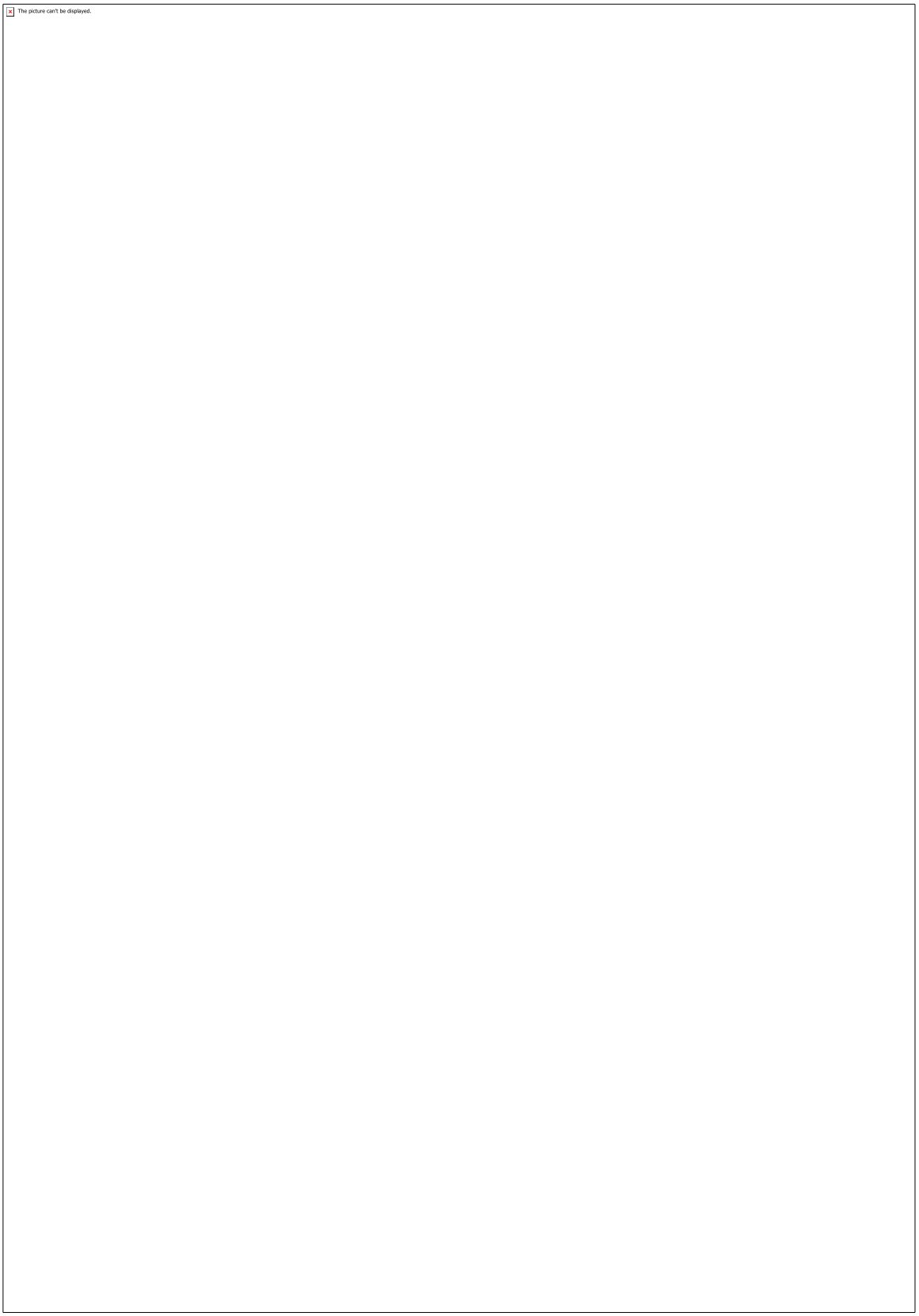
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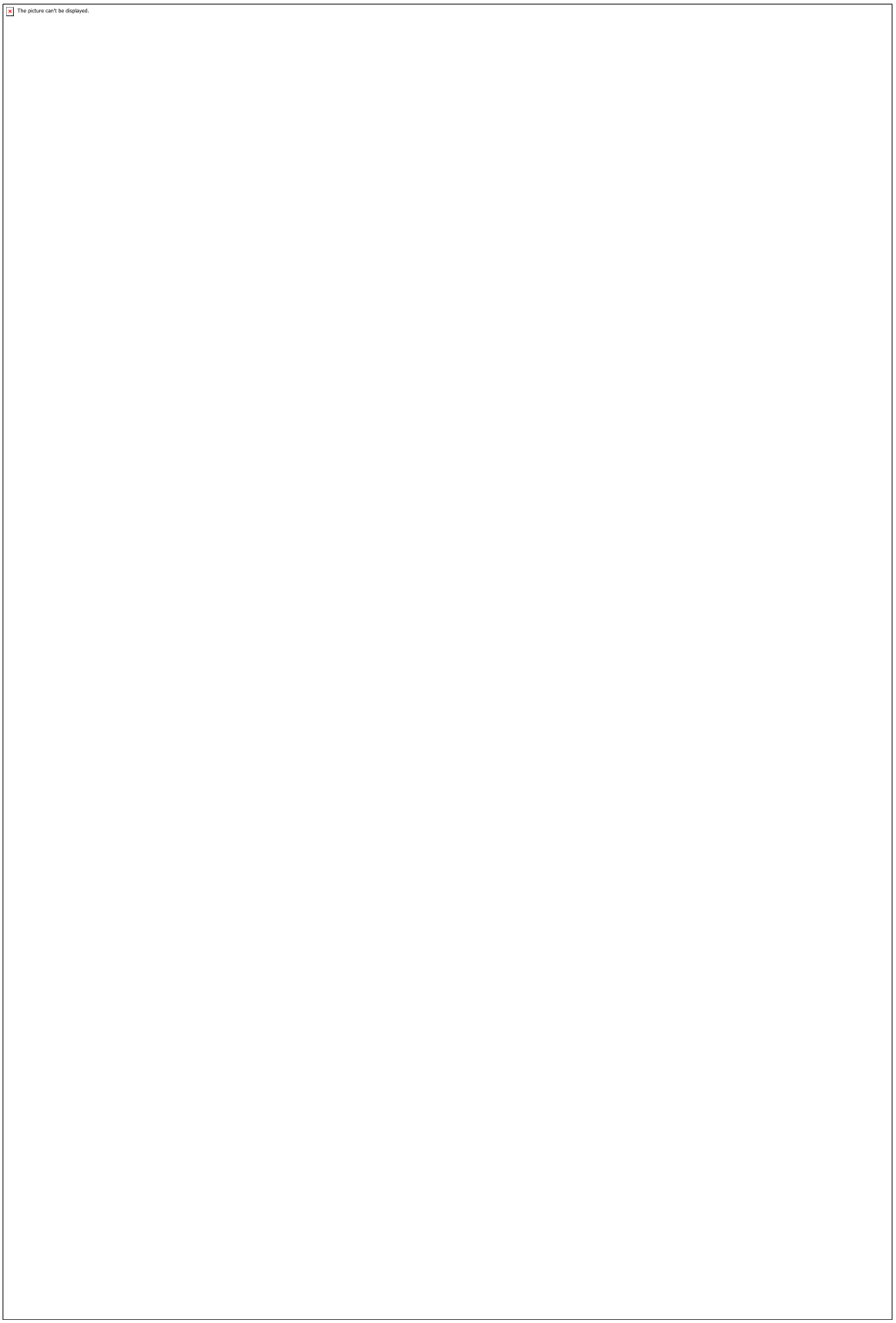
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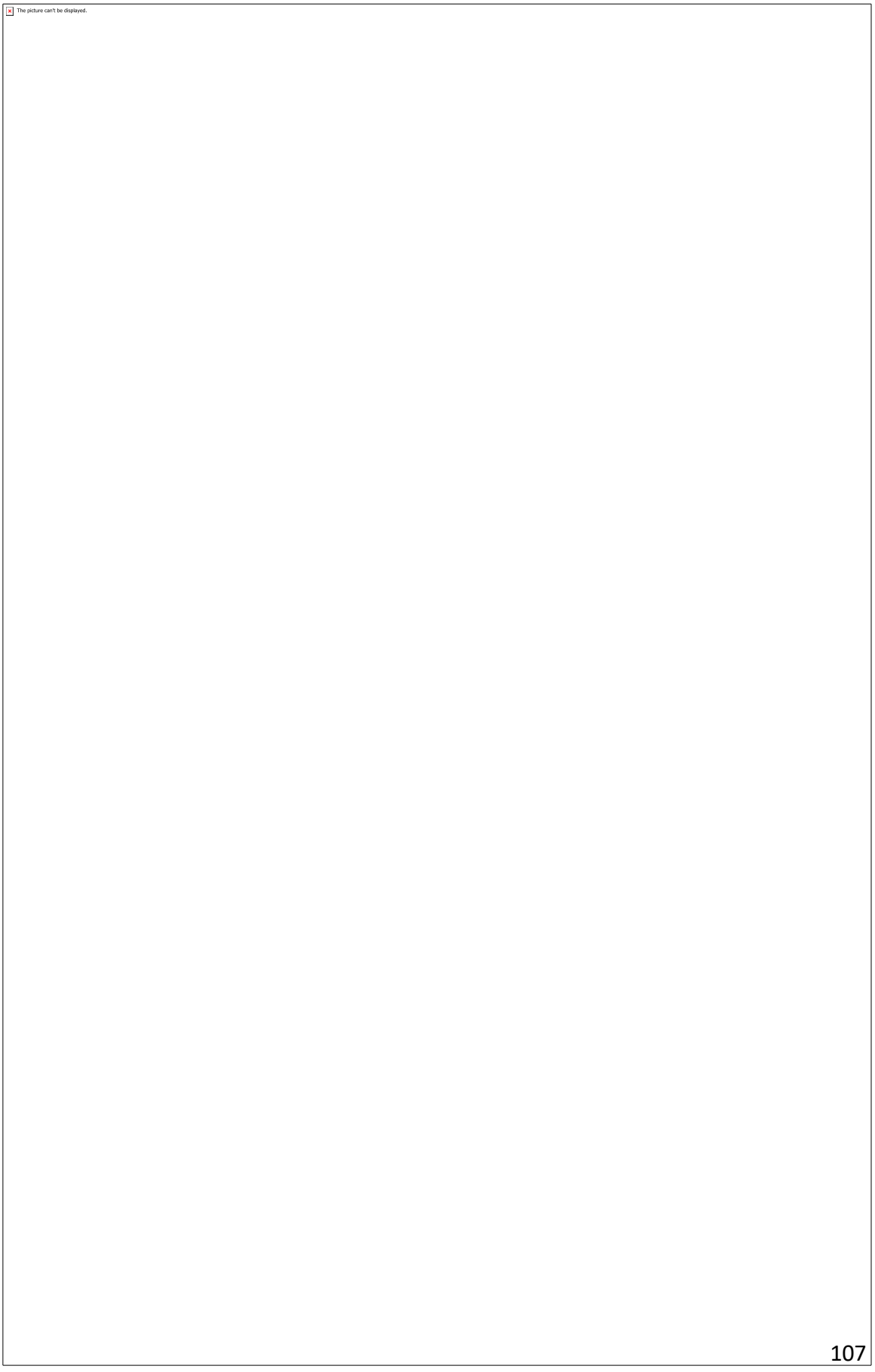
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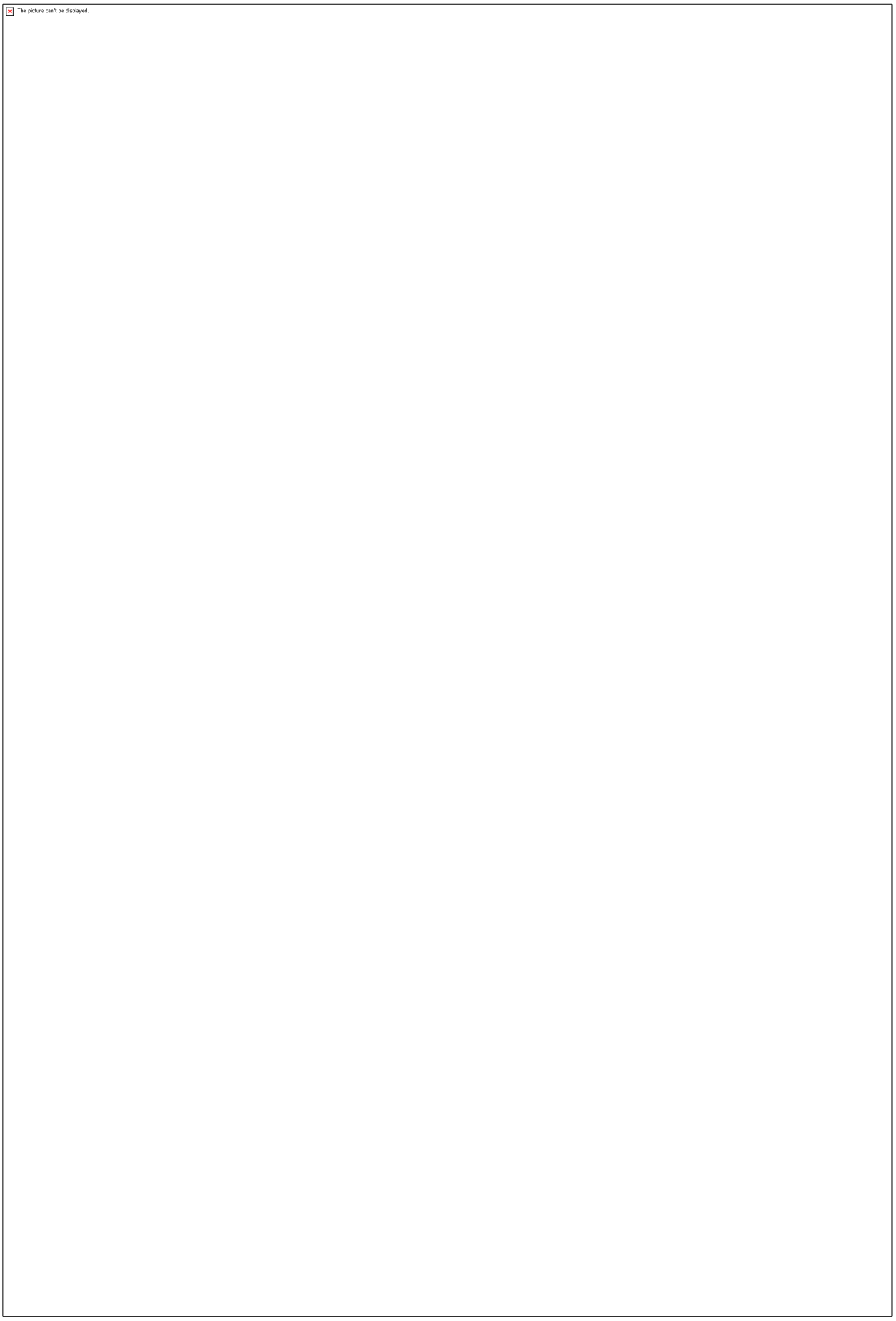
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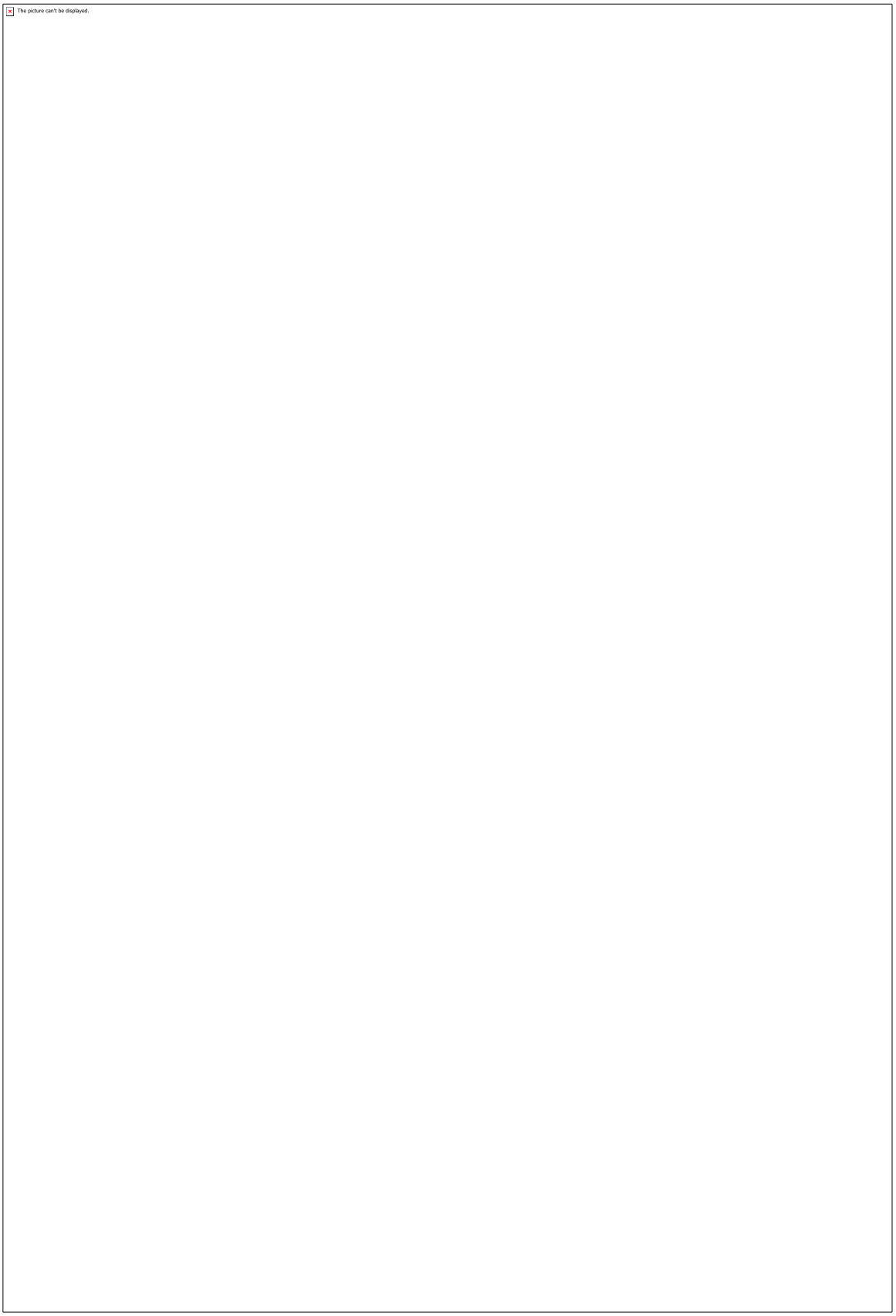
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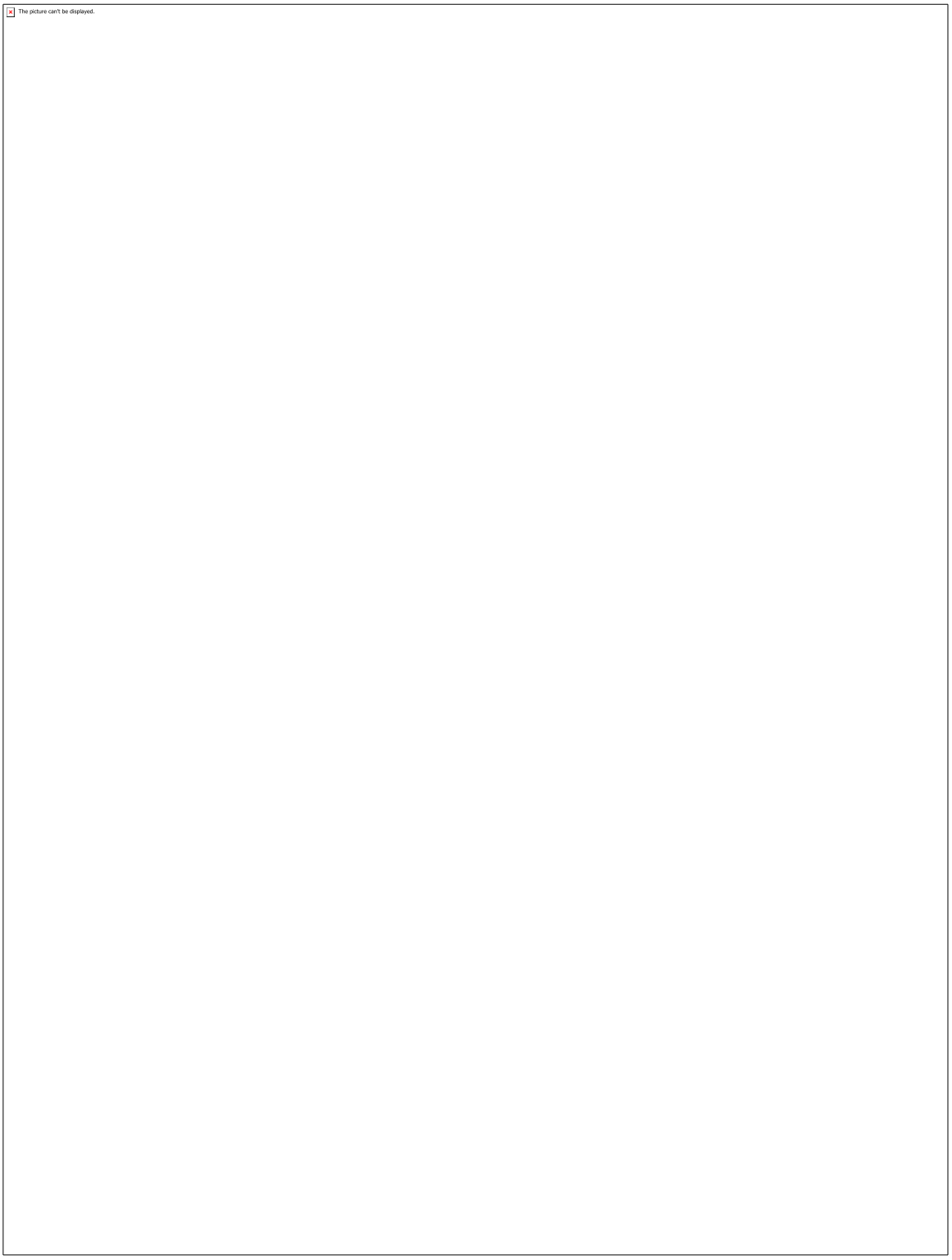
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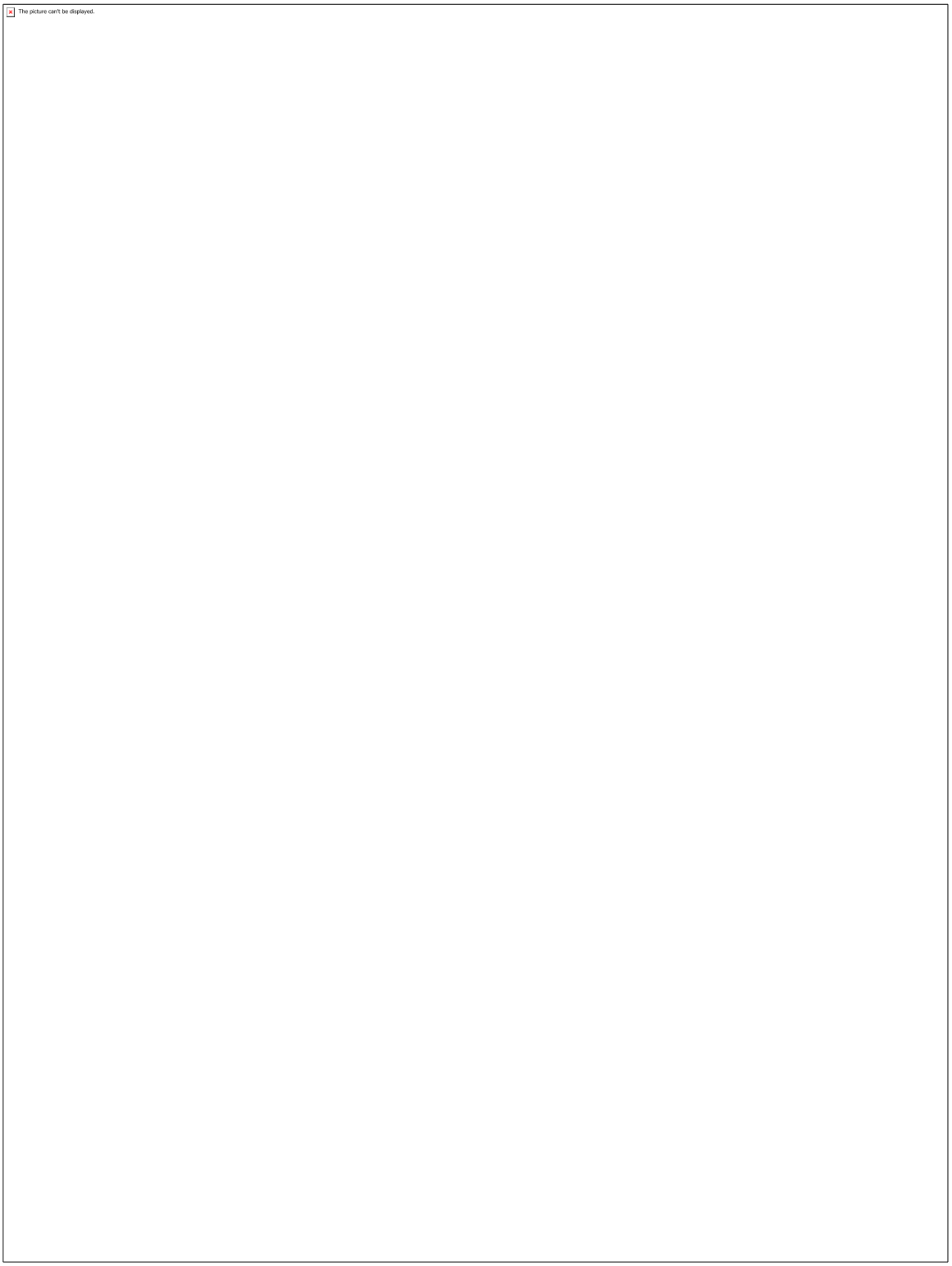
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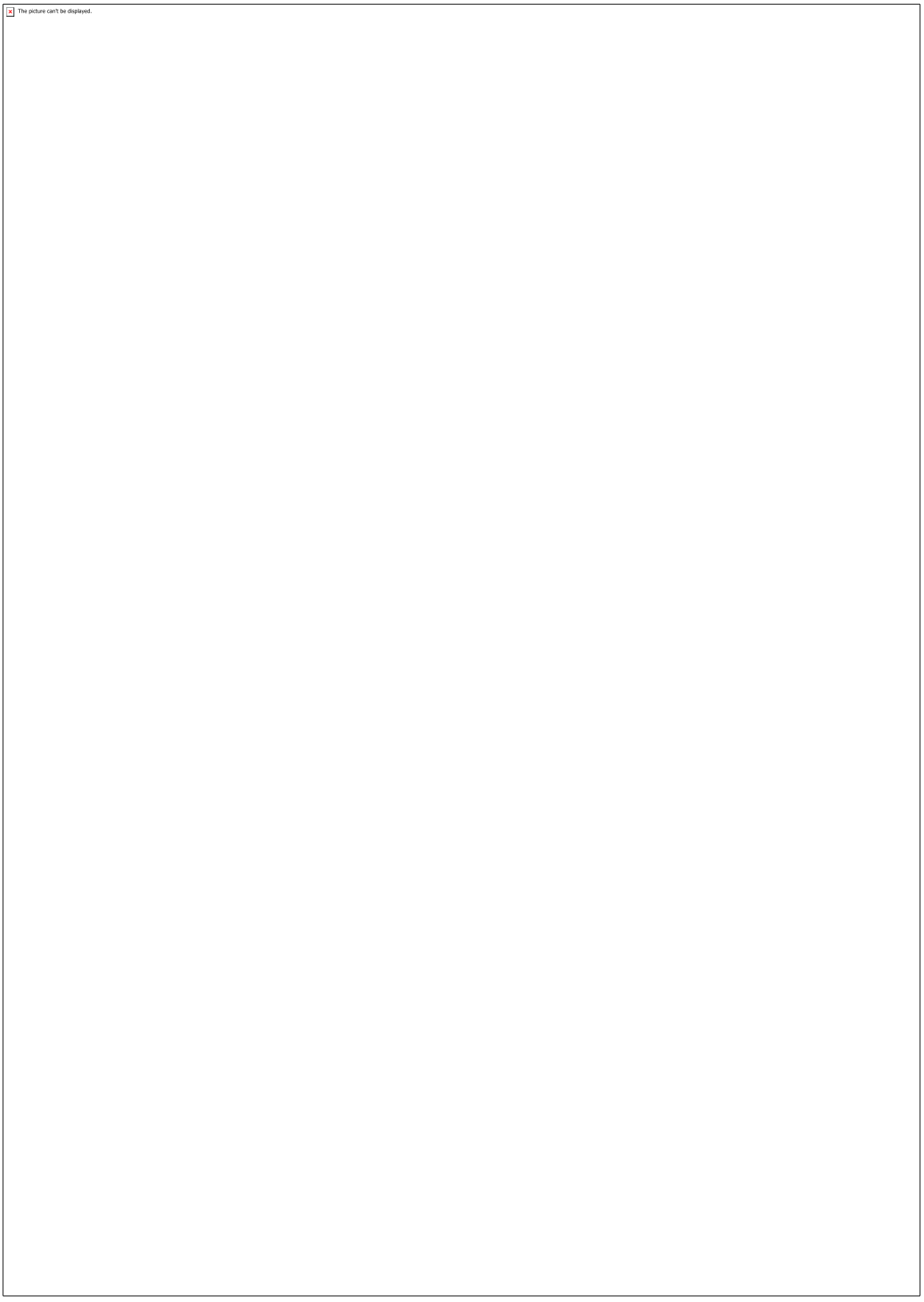
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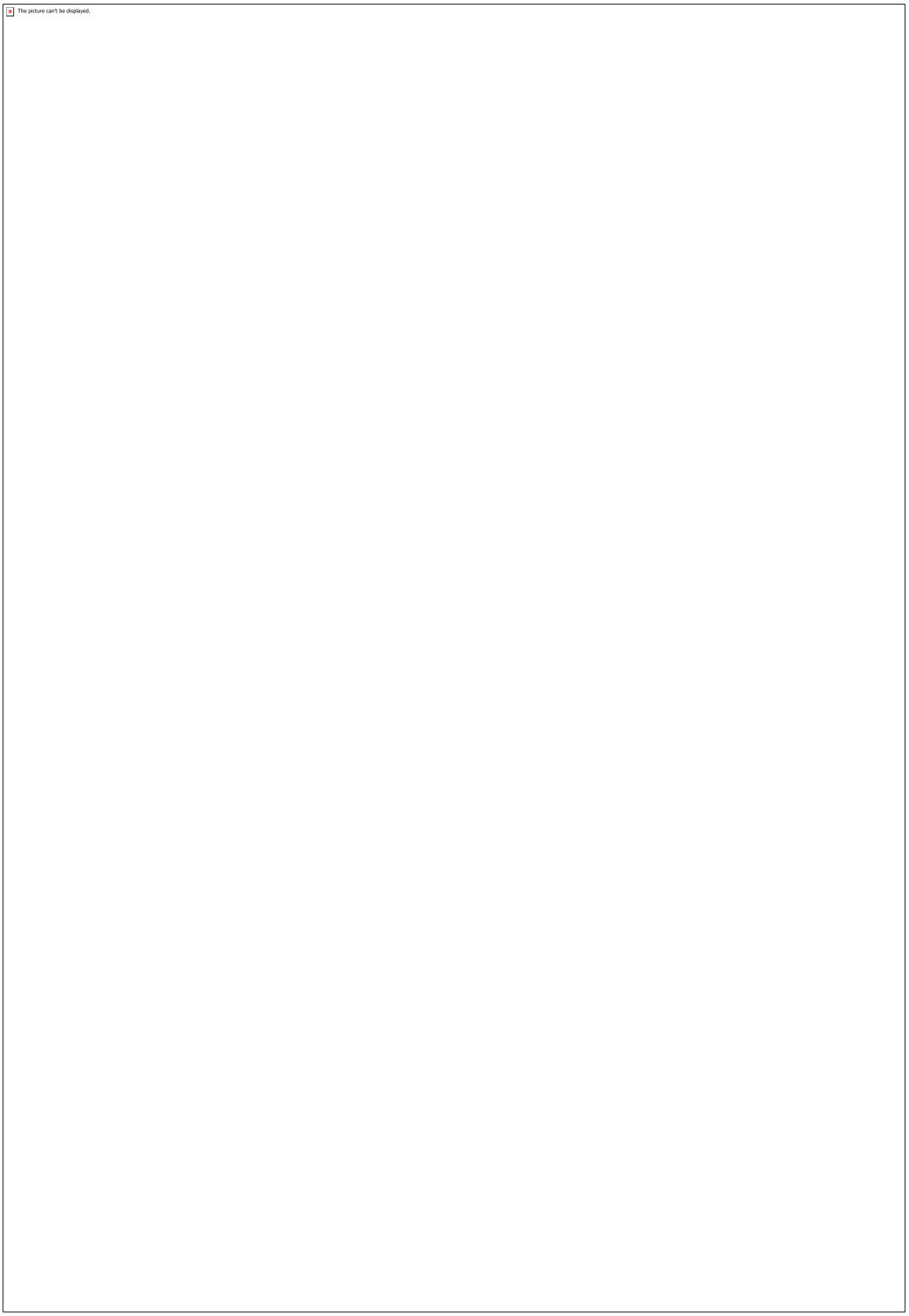
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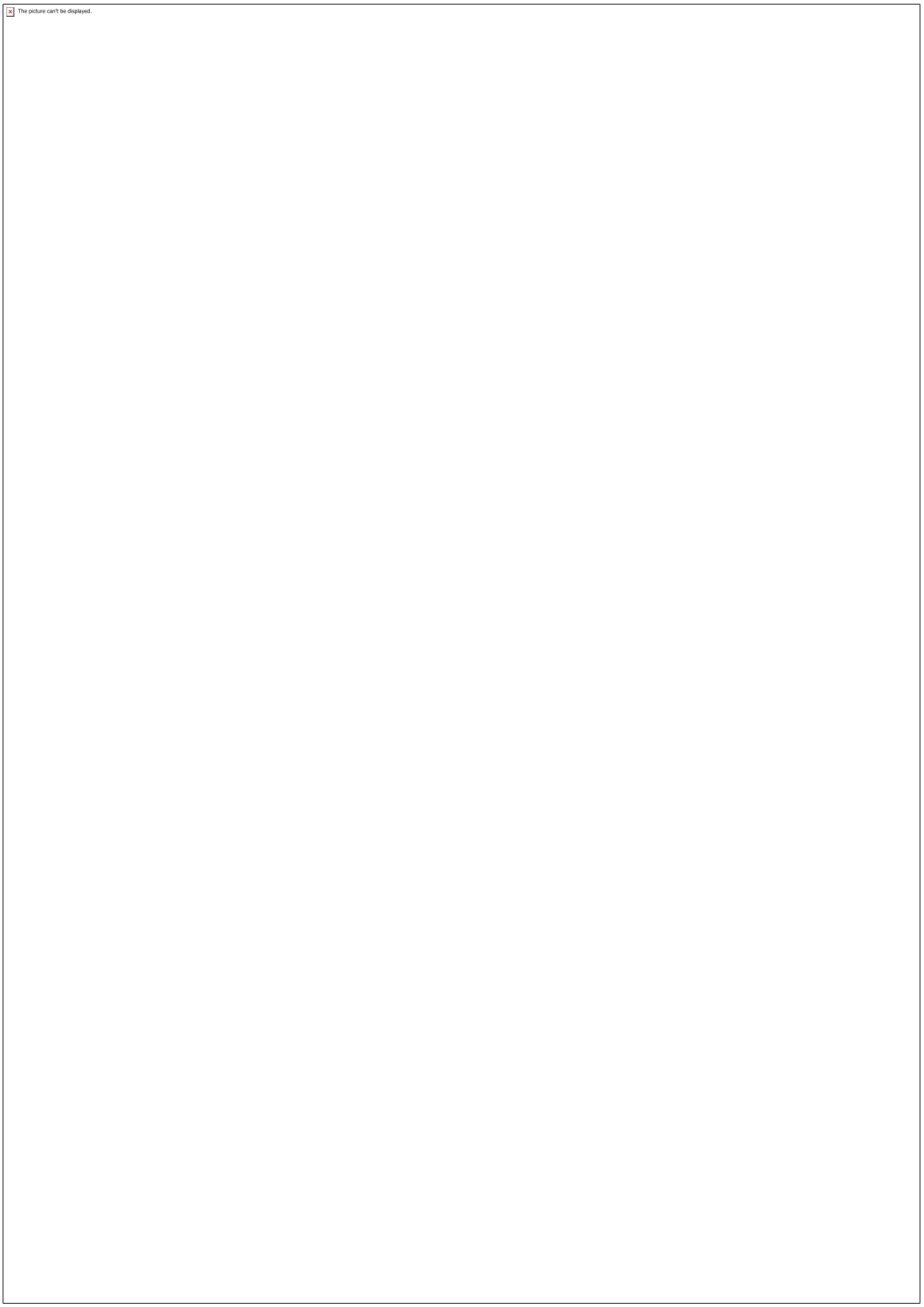
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Dexmedetomidine given intravenously is devoid of clear CNS activity up to 0.001 mg/kg in mice and rats; at higher doses (≥ 0.003 mg/kg), dexmedetomidine induced clear CNS depressant effects.

Pharmacokinetics
In beagle dogs, dexmedetomidine was rapidly eliminated following a 50 mcg/kg IV dose with a mean apparent $t_{1/2}$ of 0.68 hour; plasma elimination $t_{1/2}$ was slightly longer following intramuscular (IM) dosing.

Rats administered an intravenous 20 mcg/kg dose of [^{3}H]dexmedetomidine showed drug-related radioactivity widely distributed throughout the body, with the highest mean concentrations in blood, plasma, and selected tissues occurring from 0.25 to 12 hours postdose.

[^{3}H]dexmedetomidine was extensively metabolized by rats. Less than 1% of the dose was excreted in the urine as the parent drug. Major urinary metabolites included the COOH, OH, G-OH, SO_3OH, M-2, and M-5 metabolites. Levels of the SO_3OH metabolite were greater in female urine than in male urine. Fecal patterns generally resembled those found in urine.

The metabolism of [^{3}H]dexmedetomidine in beagle dogs was similar to that observed in rats. Biliary excretion of [^{3}H]dexmedetomidine following IV and SC administration was studied in rats with an implanted bile-duct cannula; an average of 51.6% and 45.4% of the radioactive dose was recovered in rat bile 24 hours after IV and SC administration, respectively. Major biliary metabolites were the glucuronide of a hydroxylated metabolite (G-OH) and an unidentified conjugate, M-2. Unidentified metabolites represented 12% to 18% of the dose.

Lacteal excretion, tissue distribution, and placental transfer of radioactivity were studied in rats following administration of a 0.015 mg/kg SC dose of [^{3}H]dexmedetomidine. Radioactivity was distributed in maternal tissues and crossed the placenta to distribute in fetal tissues. Drug-related radioactivity was detected in the milk of dams at 0.5 hours and reached a maximum mean concentration at 4 hours. Thereafter, levels of radioactivity in milk decreased to non-detectable levels at 72 hours. The milk:plasma concentration ratio was less than 1 at all collection time points, indicating that radioactivity did not accumulate in the milk.

TOXICOLOGY

Acute Toxicity
The highest non-lethal dose by intravenous injects was 1000 mcg/kg in mice, rats and dogs in both sexes.

In a rat neurotoxicity study, Day 7 postnatal rat pups subcutaneously injected with Precedex® (3 mcg/kg or 10 mcg/kg or 30 mcg/kg), did not produce significant degeneration in the limbic thalamic nuclei and limbic cortical regions compared to ketamine (20 mg/kg), which resulted in significant neuronal cell death and degeneration. This was determined by histological staining

(silver, Fluoro-Jade B, and Caspase-3) to detect neuroapoptosis and neurodegeneration in postnatal rat pup brains.

Long-Term Toxicology
A two-week IV infusion study in adult dogs was performed to investigate the potential effect of dexmedetomidine on toxicologic, pathologic, and hormone secretion parameters. Dexmedetomidine at 50 or 100 mcg/kg/day was well-tolerated, with treatment-related effects (sedation, hypothermia (↓ 3-4°C)) reversed by the end of the recovery period. Dexmedetomidine increased cortisol secretion, decreased LH secretion in males, decreased TSH secretion, and at the 100 mcg/kg/day dose level, decreased ACTH-stimulated cortisol secretion.

Rats receiving dexmedetomidine by IV administration for four weeks at doses up to 160 mcg/kg/day showed sedation and piloerection occurring at all doses, with exophthalmos observed only at the highest dose. No deaths occurred. Based on the drug-related small decreases in thymus and body weights at 160 mcg/kg/day, the no-toxic-effect-dose (NTED) of dexmedetomidine was determined to be 40 mcg/kg/day.

Carcinogenicity
Animal carcinogenicity studies have not been performed with dexmedetomidine.

Genotoxicity
Dexmedetomidine was not found to be mutagenic in the Ames *Salmonella* and *E. coli* assays, L5178/$tk^{+/-}$ mouse lymphoma assay, in vitro human lymphocyte cytogenics assays, and in vivo mouse micronucleus assays. No structural or numerical chromosome aberrations were noted in the presence or absence of metabolic activation. Dexmedetomidine did not demonstrate clastogenic activity.

Reproductive Toxicology
Reproductive and developmental toxicity studies were performed with dexmedetomidine in rats and rabbits.

A fertility study (Segment I) in rats at doses up to 54 mcg/kg/day administered subcutaneously showed that the No-Observed-Adverse-Effect Level (NOAEL) for F0 males and females was 54 mcg/kg/day for fertility indices and 6 mcg/kg/day for systemic toxicity. The NOAEL for F1 development was considered to be at 6 mcg/kg/day.

In a prenatal monkey neurotoxicity study, infusion of Precedex to pregnant monkeys at doses up to 30 mcg/kg/hr (10X Human Equivalent Dose) for 12 hours did not induce neuroapoptosis in fetal monkey brains compared to controls. In the same study, infusion of ketamine at 20-50 mg/kg/hr for 12 hours to mothers resulted in significant neuroapoptosis in fetal monkey brains. This was determined by immunohistochemical staining for activated caspase 3 and TUNEL in fetal monkey brains.

Teratogenic effects were not observed following administration of dexmedetomidine at subcutaneous doses up to 200 mcg/kg in rats from day 5 to day 16 of gestation and intravenous doses up to 96 mcg/kg in rabbits from day 6 to day 18 of gestation. The dose in rats is

approximately 2 times the maximum recommended human intravenous dose on a mcg/m^2 basis. The exposure in rabbits is approximately equal to that in humans at the maximum recommended intravenous dose based on plasma area-under-the-curve values. However, fetal toxicity, as evidenced by increased post-implantation losses and reduced live pups, was observed in rats at subcutaneous dose of 200 mcg/kg. The no-effect dose was 20 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m^2 basis). In another reproductive study when dexmedetomidine was administered subcutaneously to pregnant rats from gestation day 16 through nursing, it caused lower pup weights at 8 and 32 mcg/kg as well as fetal and embryocidal toxicity of second generation offspring at a dose of 32 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m^2 basis). Dexmedetomidine also produced delayed motor development in pups at a dose of 32 mcg/kg (less than the maximum recommended human intravenous dose on a mcg/m^2 basis). No such effects were observed at a dose of 2 mcg/kg (less than the maximum recommended intravenous dose on a mcg/m^2 basis). Placental transfer of dexmedetomidine was observed when radiolabeled dexmedetomidine was administered subcutaneously to pregnant rats.

In rabbits, the influence of dexmedetomidine on teratogenicity (Segment II) after IV administration in doses up to 96 mcg/kg/day was investigated. The NOAEL was 96 mcg/kg/day for maternal toxicity and 96 mcg/kg/day for F1 development. No higher dose was feasible. No teratogenicity was observed in any dose level tested.

Prenatal and postnatal development (Segment III study) was examined in rats at doses up to 32 mcg/kg/day administered subcutaneously. The NOAEL was 8 mcg/kg/day for maternal toxicity and 2 mcg/kg/day for F1 development.

Local Tolerance Studies
A solution of dexmedetomidine was shown to be mildly irritating in rats when injected intramuscularly.

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PART III: CONSUMER INFORMATION

PrPrecedex®
Dexmedetomidine Hydrochloride for Injection
Dexmedetomidine Hydrochloride Injection

This leaflet is part III of a three-part "Product Monograph" published when Precedex® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Precedex®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Precedex® is used in adults:
- for continuous sedation (to keep you calm) after you arrive at the intensive care unit after your surgery under a general anesthesia
- for sedation when you receive certain surgical procedures under a local anesthesia or nerve block or when you receiving a breathing tube while awake

What it does:
Precedex® acts by activating a part of the brain which helps keep you calm.

When it should not be used:
You should not be given Precedex® if you:
- are allergic to dexmedetomidine hydrochloride or to any non-medicinal ingredient in the formulation.

What the medicinal ingredient is:
dexmedetomidine hydrochloride.

What the nonmedicinal ingredients are:
sodium chloride and water for injection. Precedex® is preservative-free and contains no additives or other chemicals.

What dosage forms it comes in:
Precedex® is available as:
- A solution containing 100 micrograms/mL of dexmedetomidine that will be further diluted into saline and given to you by intravenous infusion. The Precedex® concentrate solution is available in a 2 mL glass vial.

- A solution containing 4 micrograms/mL of dexmedetomidine that is ready to use. No dilution is required. The Precedex® ready to use solution is available in 20 mL, 50 mL and 100 mL glass vials.

WARNINGS AND PRECAUTIONS

Precedex® should only be administered by healthcare professionals skilled in the management of patients in the intensive care unit or operating room setting.

BEFORE you are given Precedex® talk to your doctor or nurse if you:
- have heart problems, including chronic high blood pressure
- have diabetes mellitus
- have liver problems
- have severe kidney problems
- are taking any other medicines
- are dehydrated or suffer from excessive vomiting, diarrhea, or sweating
- are older than 65 years of age
- are pregnant or think you might be pregnant
- are breastfeeding

INTERACTIONS WITH THIS MEDICATION

As with most medicines, interactions with other drugs are possible. Tell your doctor, nurse, or pharmacist about all the medicines you take, including drugs prescribed by other doctors, vitamins, minerals, natural supplements, or alternative medicines.

IMPORTANT: PLEASE READ

Drugs that may interact with Precedex® include:
- anesthestic drugs such as: sevoflurane, isoflurane, propofol, alfentanil, and midazolam
- neuromuscular blockers such as rocuronium, cisatracurium
- heart medications

PROPER USE OF THIS MEDICATION

Usual Adult dose:
Dosage will be individualized and titrated to the desired clinical effect. You will be given a loading dose followed by a maintenance dose, specific for your body weight and the procedure you are undergoing. Your doctor will decide what the appropriate dose is for your specific case.

Your doctor and/or nurse will monitor blood pressure, heart rate and oxygen levels, both continuously during the infusion of Precedex® and as clinically appropriate after discontinuation.

It is important that following the return of consciousness, you do not attempt to change position or rise from bed without assistance.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

You should report symptoms that may occur within 48 hours after you are given Precedex® such as: dry mouth, nausea, vomiting, or fever.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM	
After exposure to Precedex®, you should contact your physician or anesthesia professional if you have any of the following reactions:	
Symptom / effect	
Common	
Hypotension (low blood pressure): dizziness, fainting, light-headedness	Call your doctor immediately or 911.
Hypertension (high blood pressure): headaches, vision disorders, nausea and vomiting	
Hyperglycemia (high blood sugar): irregular heartbeats, muscle weakness and generally feeling unwell	
Hypokalemia(low potassium blood level) : irregular heartbeats, muscle weakness and generally feeling unwell	
Bradycardia: slow heart beat	
Tachycardia: fast heart beat	
Hypoxia: blueish colouration to the skin, confusion, fast heartbeat, shortness of breath, sweating	

IMPORTANT: PLEASE READ

Uncommon	
Nervousness	Talk with your doctor.
Headaches	
Agitation	
Weakness	
Confusion	
Excessive sweating	
Weight loss	
Abdominal pain	
Salt cravings	
Diarrhea	
Constipation	
Dizziness/ Lightheadedness	
Anemia: fatigue, loss of energy, weakness, shortness of breath	
Respiratory difficulty	Call your doctor immediately or 911.

This is not a complete list of side effects. For any unexpected effects while taking Precedex®, contact your doctor or pharmacist.

HOW TO STORE IT

Precedex® (100 mcg/mL) is stored between 15 to 30°C.
Precedex® (4 mcg/mL) is stored between 15 to 30°C.

Protect from freezing.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways.

- Report online at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html.
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
  Health Canada
  Postal Locator 1908C
  Ottawa, Ontario
  K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor Pfizer Canada Inc. at: **1-800-463-6001**.

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