The use of Dipyrone in Pre-emptive and Postoperative Analgesia in Tonsillectomy in Children: A Systematic Review

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Abstract

Tonsillectomy is the most common surgery in children. Post-tonsillectomy pain is universal and associated with considerable morbidity. Dipyrone is banned in some countries and the analgesic most commonly used in others. Evidence of the effectiveness of dipyrone in postoperative analgesia of tonsillectomy are scarce. Serious adverse effects such as agranulocytosis and anaphylaxis are rare and their incidence varies in different populations.

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Introduction:

Acute postoperative pain is the pain present in surgical patients following the procedure[1]. Pre-emptive analgesia describes the attempt to control pain in the pre-incisional period. It aims to prevent central hyperexcitability, which tends to amplify in the postoperative period[2]. A recent review of systematic reviews concluded that evidence for the efficacy of various drugs and strategies for managing postoperative pain in children is still inconclusive[3]. Dipyrone, however, was not evaluated in this review.

Dipyrone is effective in postoperative pain in children. There are 8 clinical trials that have used it alone or in combination with other medications[4-11]. It is one of the most widely-used analgesics in the postoperative period in several European[12-13], African[14] and Latin American countries[15]. However, there is concern about its potential for associated anaphylaxis and agranulocytosis[16]. Its use is banned in more than 20 countries.

The real incidence of these adverse effects, however, is low. In a multicentre study involving more than 1,177 children treated with dipyrone in the postoperative period, the incidence of serious adverse effects was less than 0.3%, with no case of agranulocytosis[17]. Two studies, one involving several European countries (Germany, Italy and Spain)[18] and another only in the city of Berlin[19], estimated an incidence of agranulocytosis of 1.1 per million inhabitants/year and 0.96 cases per million inhabitants/year, respectively. In the city of Barcelona, the estimate was 0.56 cases per million inhabitants/year[20]. The risk of severe complications and the availability of alternatives continue to contraindicate its use in the opinion of some[21]. Despite the ban in several countries, dipyrone is the most widely used painkiller in the postoperative period for children in Brazil, perhaps due to its low cost and the lack of an injectable form of paracetamol, at least until April 2020[22]. In terms of oral analgesic medication, in contrast with the preference for paracetamol in different regions of the world[23], in our country it is the most widely-used self-medication, as it is sold as an over-the-counter medicine[24].

Dipyrone has been used for decades in children in the postoperative period of tonsillectomy. This surgery is the 2nd most common outpatient procedure in the USA[25,26]. Its main complication is pain that can lead to a reduction in oral intake, dehydration and weight loss[27]. The latest North-American Clinical Practice Guideline on Tonsillectomy contains 2 strong recommendations about analgesia: 1. to use analgesics in the post-operative period and 2. the contraindication in the use of opioids, especially in children under 12[27]. This latter recommendation is based on the FDA's warning of the risk of respiratory depression and death using codeine[28]. In context of tonsillectomy, intravenous dipyrone could represent an alternative to opioids, where odynophagia with consequent difficulty in swallowing is almost universal.

The aim of this study was to review the analgesic use of dipyrone in the postoperative period of tonsillectomy in children.

Materials & Methods:

This study is a systematic review of the literature, which involved the work of two researchers independently evaluating the quality of each article. The formulation of the research question was based on the PICO strategy[29]. The following questions guided the bibliographic search: Is the action of dipyrone indicated for pre-emptive or postoperative analgesia in tonsillectomy in children? Are there any positive or negative influences? The search was carried out in the databases MEDLINE / PubMed, EMBASE and Virtual Health Library (VHL / Lilacs), using separate and combined terms, with the Boolean operator OR and, using the following subject descriptors in health sciences from BIREME (DeCS): dipyrone OR metamizole AND postoperative pain; dipyrone OR metamizole AND postoperative pain AND children, dipyrone OR metamizole AND tonsillectomy, dipyrone OR metamizole AND tonsillectomy AND children, dipyrone AND metamizole AND pre-emptive analgesia, dipyrone OR metamizole AND pre-emptive analgesia AND children. Additionally, the references of the selected articles were reviewed in the search for other relevant publications. The selection of articles was carried out in the months of June / 20 and July / 2020.

The inclusion criteria were as follows: studies that addressed the treatment of pain with dipyrone in a pre-emptive way or after the end of surgery in children. This was then refined for studies with a randomised clinical trial design and that dealt exclusively with tonsillectomies, with dipyrone alone or in combination with another drug in one of the comparison groups. There was no time limit for publications, and we included all articles available in full in Portuguese, English, Spanish and German. As exclusion criteria, the following were adopted: publications corresponding to theses, dissertations, abstracts of congresses and annals and all articles that exclusively included evaluation of chronic pain and studies in adults.

The studies were classified according to the level of evidence, following the Oxford Centre for Evidence Based Medicine recommendations[30]. The studies were also described according to the GRADE[31] classification, which takes into account the quality of the evidence (high or level A, moderate or level B, low or level C and very low or level D) and the degree of recommendation (strong or weak). Finally, the two included studies were classified according to the Jadad[32] scores, which assess the methodological quality of the study using specific criteria: poor (scores 0-2), good (3-4) or excellent (score 5 or more). The PRISMA strategy (Preferred Reporting Items for Systematic Reviews and Meta-Analysis)[33] was used in this review in order to qualify the work when performing a critical analysis of the selected studies. Figure 1 shows the flowchart of identification, selection and inclusion of studies based on the PRISMA recommendation.

(**Figure 1:** PRISMA flowchart)

Results:

The maximum number of 1151 articles were selected using the descriptors "dipyrone or metamizol and postoperative pain". The number of articles found in EMBASE was 1,151, in PUBMED 336 and in VHL 345. When the descriptor "children" was introduced to the previous search, the corresponding numbers were 120, 49 and 42. When adding "randomised clinical trial", the corresponding numbers were 31, 13 and 19. It was decided not to use the last search and the abstract, and the materials and methods of each article obtained from the search with the descriptors "dipyrone or metamizole and postoperative pain and

children" were manually reviewed. Nine randomised clinical trials were identified evaluating the postoperative analgesic effect of dipyrone in isolation or associated with one of the groups. When only studies dealing with tonsillectomy were selected, 3 remained and it was seen that there was a duplicate of one. The final search result was 2 randomised clinical trials that evaluated the effect of dipyrone against placebo, one in pre-emptive and the other in the postoperative analgesia, in children undergoing tonsillectomy, with or without adenoidectomy or placement of ventilation tubes.

Tables 1, 2 and 3 show information on the 2 articles included. Table 1 shows the study identification, investigational model, follow-up time, inclusion criteria, age, sex and the sample size.

(Table 1: Characteristics of selected articles.**)**

The studies had short follow-up times (maximum 24 hours). While the first study involved only older children, the second study included children from 3 years old. While in the first study, only cases of isolated tonsillectomy were evaluated, in study 2, tonsillectomy either with or without associated adenoidectomy and / or placement of ventilation tubes was allowed.

Table 2 shows the description of the data referring to the intervention groups (random number and number who completed the study in each group), type of analgesia and form of administration of dipyrone. Both studies had a 100% completion rate for the randomised sample. While in the first study analgesia was post-operative, in the 2nd it was applied pre-emptively, thus, making it difficult to directly compare the two studies. The first study brought an innovation to the paediatric surgery postoperative period, in the use of PCA (patient-controlled analgesia).

(Table 2: Description of the intervention groups, type of analgesia and form of administration of dipyrone.**)**

Table 3 describes the strengths and weaknesses of each study, the primary and secondary outcomes, the results, the level of evidence according to Oxford criteria, the levels of evidence and degrees of recommendation according to the GRADE classification and the Jadad scores.

(Table 3: Strengths and weaknesses, primary and secondary outcomes, main results and Oxford, GRADE and Jadad classifications of studies.**)**

It is evident that both studies demonstrated care in their methodological approach. For this reason, the Jadad classification for the first paper was excellent (score = 5) and the second was classed as good (score = 4). The study by Kocum et al. lost a point for not explicitly describing withdrawals and losses. The other classifications were equal for both studies. Regarding the analgesic results measured by validated pain scales in childhood, dipyrone and paracetamol were superior to placebo and similar to each other in many measured intervals. The same was observed for the use of rescue pethidine, and this did not differ between active comparison groups.

Discussion:

1) Effectiveness of miscellaneous analgesics with emphasis on dipyrone in the post-operative period of tonsillectomy in children:

Dipyrone has an efficacy, measured by the number of patients needed to treat to achieve a 50% reduction in postoperative pain in 4 to 6 hours, that is lower than potassium diclofenac and etoricoxib, but greater than several NSAIDs (paracetamol, naproxen, ibuprofen, celecoxib, aspirin and sodium diclofenac). Unfortunately, all these estimates are for adults, and there are no similar studies in children[34]. There is one systematic review specifically evaluating the efficacy of dipyrone in postoperative pain in children[35]. Ten systematic reviews were identified regarding postoperative analgesia in tonsillectomy performed in children. The first studied the use of systemic paracetamol, NSAIDs and opioids. However, it did not comment on dipyrone[36]. Two analysed the effect of ketamine via peritonsillar or systemic injection[37,38], two studied the effect of corticosteroids[39,40], one focused on the effect of bupivacaine[41] and the other on dexmedetomidine compared to morphine or fentanyl[42]. A Cochrane systematic review analysed the form of analgesic prescription (different analgesics, but never dipyrone), if required or fixed[43]. Finally, there was another review that was restricted

to the use of oral rinses and sprays to improve recovery followed by tonsillectomy[44]. An overview of all these systematic reviews was given in the recent work by Boric et al., 2017[3].

As demonstrated in the present review, there are only two randomised clinical trials that have evaluated the analgesic effect of dipyrone in the postoperative period of tonsillectomy in children[6,7]. Unfortunately, it was not possible to perform a meta-analysis, as one study included isolated tonsillectomy[7] and the other allowed associated adenoidectomy and / or ventilation tubes[6], which can lead to different levels of pain, due to the greater manipulation of the patients. In addition, one study evaluated preemptive[6]and the other postoperative analgesia[7]. Finally, the study of pre-emptive analgesia gave a single dose of dipyrone or placebo right after introduction of the anaesthetic[6], while the other study evaluated analgesia initiated in the postoperative period through the use of PCA[7]. The limitation is that PCA is not available in most hospitals and requires the understanding and collaboration of the patient, thus being ineffective for young children.

Both studies demonstrated adequate methodological care, with sample size calculations, and with randomisation performed through the website randomization.com. Moreover, hypotheses were established a priori, with the use of a placebo with the same characteristics as the active medication, with adequate blinding of both patients and examiners, and with effective and validated outcome measures, in addition to a careful choice of the statistical tests used. Together with another study dealing with abdominal surgery[5], they comprise the 3 clinical trials with the best level of evidence of all studies commented here, according to the Oxford classification, the GRADE system or the Jadad scores.

However, the studies have short follow-up times (maximum 24 hours). It would be preferable to have a longer follow-up time to monitor the effect of dipyrone, as the pain after tonsillectomy persists for at least 7 days. Another limitation of the results is that, in addition to being developed by the same group of researchers and not being able to be combined for a meta-analysis for the reasons already specified, the data have never been replicated elsewhere by different researchers, which can limit the extrapolation of data to populations other than Turkish patients.

2) Agranulocitose:

Agranulocytosis is defined as an absolute circulating neutrophil count of less than 500 / µl[45]. The most common clinical course of agranulocytosis is associated with pharyngotonsillitis, stomatitis and / or pneumonia. The frequency of the disease varies with age, with only 10% of cases being reported in children and young adults, and more than half of the episodes occurring in people over 60 years of age. It is a rare condition and is associated with a fatality rate of 8 to 10%. Association rates with drug use vary in the different studies, but in Brazil, for example, it is around 56%[46].

No randomised clinical trials using dipyrone as a postoperative analgesic in children have reported the occurrence of agranulocytosis to date. Studies show that the incidence of agranulocytosis varies between countries. The LATIN[46] study was a prospective case-control study carried out in cities in Brazil, Argentina and Mexico. The overall incidence rate was estimated at 0.38 per million inhabitants/year. Methimazole was the only drug significantly associated with agranulocytosis ($p < 0.001$), and there was no significant association with dipyrone. A rare incidence of agranulocytosis associated with drugs has been reported in a retrospective study in the city of São Paulo / Brazil (0.44 to 0.82 cases per million inhabitants / year)[47] and in the collaborative study of Brazil, Argentina and Mexico mentioned above, similar to the finding in Thailand - 0.8:1 million inhabitants/year[48]. This contrasts with the higher incidence reported in the United States of America, from 2.4 to 15.4 per million inhabitants / year[49], and in European countries, such as that of the collaborative study in Germany, Italy, Spain, Hungary, Bulgaria and Sweden, in addition to Israel, which found 1.1 to 6.2 cases / million / year and a mortality rate of 0.5 cases / million / year. However, this study noted a great regional variability in the presentation of blood dyscrasias[50]. The risk was significantly associated with the use of ticlopidine, sulphonamides, non-steroidal anti-inflammatory drugs, calcium dobesilate, antithyroid drugs, spironolactone and dipyrone. There was a subsequent study, in the city of Barcelona, which found an incidence of agranulocytosis associated with medications in the order of

3.46 cases per million inhabitants / year[20]. In France, the corresponding number was 6 cases per million inhabitants / year[51]. The specific incidence of agranulocytosis associated with dipyrone varied from one for every 1,439 prescriptions in Sweden36, to 0.56 cases per million inhabitants / year in Barcelona[20], reaching up to 0.96 cases per million / year in Berlin[19]. A cohort of hospitalised patients in Bogotá, Colombia, involving 2,743 patients, showed no cases of agranulocytosis[52]. In the LATIN study[47], the odds ratio (OR) for drug-associated agranulocytosis was 2.4 (95% CI 0.8–6.7). The corresponding figures in Barcelona were 25.8 (95% CI 8.8-79.1)[20]. In a study published in 2020, the OR for agranulocytosis and drug-induced neutropenia was 3.03 (95% CI 2.49 to 3.69). The risk of developing agranulocytosis and neutropenia after a dipyrone prescription was 1:1,602 (95% CI 1:1,926 to 1:1,371)[53]. There are several possible explanations for the differences found in incidence between the various studies, ranging from the use of different methodologies to the genetic heterogeneity of populations, with probable gene polymorphisms of their own, which have not yet been studied specifically for dipyrone.

Even though the risk of agranulocytosis with dipyrone is undeniable, its real incidence in the population is not known, but it is assumed to be low. For this reason, the German consensus that brought together several representative entities concluded that dipyrone has a positive risk-benefit rate compared to other non-opioid analgesics, recommending its use[54].

Conclusion:

Although it appears that dipyrone exhibits a profile suitable for use in children, more well-designed studies are needed to establish its role in the postoperative period of tonsillectomy due to the scarcity of randomised clinical trials evaluating its postoperative analgesic effect. The argument for the occurrence of agranulocytosis does not seem strong enough to justify the abandonment of these studies, because its incidence is very low, mainly in children, at least in Latin America. Specially in low-income countries, its use is attractive because it has a low cost and can be used intravenously, an advantageous feature in the postoperative period of tonsillectomy where odynophagia is universal.

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