Received: 8 May 2020 | Revised: 22 June 2020 | Accepted: 22 June 2020

DOI: 10.1111/apa.15449

REGULAR ARTICLE

ACTA PÆDIATRICA NURTURING THE CHILD WILEY

Ibuprofen in needle procedures in children with cancer—A feasibility and pilot study

Tove Kamsvåg[1] | Lena Hedén[1,2] | Louise von Essen[3] | Gustaf Ljungman[1]

[1]Department of Women's and Children's Health, Pediatric Oncology, Uppsala University, Uppsala, Sweden

[2]Faculty of Caring Science, Work Life and Social Welfare, University of Borås, Borås, Sweden

[3]Department of Women's and Children's Health, Clinical Psychology in Healthcare, Uppsala University, Uppsala, Sweden

Correspondence
Tove Kamsvåg, Children's University Hospital, 751 85 Uppsala, Sweden.
Email: Tove.kamsvag_magnusson@kbh.uu.se

Funding information
This work was supported by the Swedish Childhood Cancer Fund, the Swedish Cancer Society, the Mary Béve Fund.

Abstract

Aim: To investigate the feasibility, and perform a pilot study, of a randomised clinical trial, investigating whether children experience less pain, fear and/or distress when they receive oral ibuprofen vs placebo before a needle is inserted in a subcutaneously implanted intravenous port.

Methods: Twenty-three children were included consecutively and randomised to either oral ibuprofen (n = 12) 7.5 mg/kg body weight or placebo (n = 11). The child's pain, fear and distress were reported by parents, nurses and the children (if ≥7 years of age). Feasibility criteria were defined as (a) ≥4 children included/month, (b) ≥80% of eligible patients agreed to participate, (c) >90% treated according to protocol, (d) <5% missing data, (e) s-cortisol samples analysed in ≥90% of the children.

Results: All feasibility criteria were met except recruitment and consent. Parents, nurses and children reported no trend of benefit of oral ibuprofen with regard to pain, fear and distress compared with placebo.

Conclusion: The study failed to meet important feasibility criteria and was closed due to low recruitment rate and absence of trend of effect. From this data, we cannot state that ibuprofen is not helpful in needle procedures but that it seems unlikely.

KEYWORDS

feasibility study, pediatric pain, procedural pain

1 | INTRODUCTION

Some children experience needle procedures such as insertion of a needle in a subcutaneously implanted intravenous port as painful, frightening and distressing even when the skin has been numbed by a topical anaesthetic.[1,2] Sometimes, children have to be restrained or sedated to carry out the procedure.[3] Our research group has previously examined the effect of non-pharmacological methods, for example distraction,[4,5] as well as pharmacological methods, for example low dose midazolam, paracetamol and morphine [5-7] in this context to reduce pain, fear and distress, in children. Fear and distress are reduced by distraction and midazolam when Eutectic Mixture of Local Anesthetics (EMLA) is used but pain is not.[5] Neither paracetamol[6] nor morphine[7] reduced fear, distress or pain.

Non-steroid anti-inflammatory drugs (NSAIDs) such as ibuprofen have an analgesic, anti-inflammatory and antipyretic effect

Abbreviations: APL, Apoteket Production & Laboratories; ASA score, American Society of Anesthesiologists' Physical Status Classification System; CHEOPS, Children's Hospital of Eastern Ontario Pain Scale; EMLA, Eutectic Mixture of Local Anesthetics; GCP, Good Clinical Practice; IG, Ibuprofen group; NSAIDs, Non-steroid anti-inflammatory drugs; PG, Placebo group; RCT, Randomised Clinical Trial; SD, Standard deviation; VAS, Visual Analogue Scale.

and are widely used to reduce mild to moderate pain in children in hospital as well as over the counter.[3,8] Ibuprofen has been shown to reduce postoperative pain in adults[9-11] and children.[12,13] Overall, ibuprofen has a good established reputation for safety and efficacy.[14] However, there are potential side effects such as allergic reactions, reduced renal function, gastrointestinal bleeding and inhibition of thrombocyte aggregation. The recommended oral dose of ibuprofen for children at the time of the study was 5.0-7.5 mg/kg body weight/dose ibuprofen. Orally administered ibuprofen has a T_{max} of 45-90 minutes in children. Execration is renal, and serum half-life is around 2 hours.[15,16] Cortisol levels as a biochemical indicator of distress have been used to assess stress response connected to children's pain.[17,18] Given that the cortisol level varies throughout day and night, increase or decrease should be compared to baseline. Cortisol levels are known to increase 15-30 minutes after a stressful stimulus.[19] To the best of our knowledge, no previous study has investigated the effect of ibuprofen on pain, fear and distress in conjunction with needle procedures in children. We were interested to investigate whether ibuprofen adds any value, over and above that of standard care, in needle procedures where the pain is short and sharp and, thus, differs from many other types of pain. The primary aims of this study were to explore the feasibility of a randomised, double-blind, placebo-controlled trial, investigating if children experience less pain, fear and/or distress when they receive oral ibuprofen vs placebo prior to needle insertion in a subcutaneously implanted intravenous port when combined with standard care, including topical anaesthetics, and to perform a pilot study to test logistics and effect trends.

Key notes

- In this feasibility and pilot study testing ibuprofen in a needle procedure, recruitment of participants was more difficult than expected mainly due to frequently met exclusion criteria.
- The predefined feasibility criteria were not reached.
- Parents, nurses and children reported no trend of benefit of oral ibuprofen with regard to pain fear and distress compared with placebo.

2 | PATIENTS AND METHODS

2.1 | Design

The study design was a feasibility and randomised controlled pilot trial.

2.2 | Participants and setting of the study

Children who were to have a needle inserted in an intravenously implanted port in a Swedish paediatric oncology and haematology setting were eligible. Exclusion criteria were as follows:

(a) Age < 1 and ≥20 years; (b) Experiencing moderate to severe pain assessed with a visual analogue scale (VAS), (>50 on a 0-100 mm scale) of other causes than the needle insertion; (c) Fever > 39°;

(d) Thrombocytes < 50 × 10^9/L; (e) Previously known severe needle phobia (with a documented need for pharmacological sedation); (f) On standing medication with ibuprofen; (g) On medication interacting with ibuprofen (eg methotrexate, tacrolimus or cyclosporine); (h) Scheduled infusion/injection of methotrexate or platinum-based compounds within 6-8 hours of needle insertion; (i) Known allergy to ibuprofen; (j) Non-Swedish speaking children and parents, (k) Need for immediate needle insertion (eg neutropenic fever).

Participants were recruited between May 2007 and September 2008. All included children had previous experience of needle insertions. The child and parent/guardian received oral and written information and were invited to participate in the study at the end of a previous hospitalisation. Written informed consent from parent/guardian was obtained, and oral informed assent was obtained from children from 4 years of age, at the time for needle insertion. The study was approved by the regional ethical review board and by the Medical Product Agency. The study is registered in the European Clinical Trial Database EudraCT (2005-005645-19) and was conducted according to Good clinical Practice.

2.3 | Randomisation and interventions

Children were randomised to either ibuprofen or placebo. Randomisation was performed by Apoteket Production & Laboratories (APL) AB, Stockholm Sweden using a computerised random number generator program. To create balanced age groups, the children were randomly stratified for age (<7 [n = 11] or ≥7 years [n = 12]). Study medication was manufactured by APL, which is a national pharmaceutical production unit, and provided in blinded 100 mL ampoules containing 20 mL oral mixture. The concentration of ibuprofen was 20 mg/mL, and the placebo was the same volume oral mixture base without active substance. Investigators, study site personnel, children, parents and monitors remained blinded to treatment allocation until the data analysis. All participating children received standard care including EMLA for ≥60 minutes at the site of needle insertion and information according to the usual routines. The same routines and material for needle insertion into the port was used during the whole study period. Routines included that the child was lying on his/her back on a stretcher, while the responsible nurse inserted the needle in the port after removing the EMLA and disinfecting the skin with Chlorhexidine antiseptic 5 mg/mL. Thereafter, an occlusive dressing was applied over the needle securing the needle position. Parents were present during the procedure encouraging their child

by, for example holding the child's hand. For standardisation, the child had food and drink restrictions 60 minutes before the ibuprofen was given. Children in the ibuprofen group received 7.5 mg/kg body weight ibuprofen, with a maximum of 400 mg, 60 minutes before needle insertion.

2.4 | Data collection

Data were collected by a study nurse and were documented in the study chart as well as in the child's medical chart.

2.5 | Criteria for success of feasibility

Criteria for success were defined as having at least four children agree to participate in the study per month, and having 90% or more of all participants treated according to protocol with a maximum of 5% missing data in total. Criteria for feasibility also included that s-cortisol was analysed in 90% or more of the children.

2.6 | Outcome measures

To study effect, the primary outcome of the study was pain during needle insertion of a subcutaneously implanted intravenous port. Other outcomes were fear and distress during insertion, pain behaviour during insertion, procedure time and s-cortisol levels in the ibuprofen compared to placebo group.

Pain, fear and distress were assessed with VAS questionnaires used by our group in earlier similar studies.[5-7] The questions included were "How much pain/fear/distress did you/your child/the child experience when the needle was inserted?" and they were to be answered on a 100 mm VAS with anchors at the extreme ends (no pain/fear/distress—worst possible pain/fear/distress). For all children, one of the parents and the nurse responsible for the needle insertion completed the VAS questionnaire 5-15 minutes after the needle insertion. The time was chosen to allow the parents time to support and, if necessary, comfort their child before they reported the VAS values. Children less than 7 year of age can have difficulties expressing pain, fear or distress with VAS.[20] Hence, only children 7 years or older were asked to report VAS values for pain, fear and distress directly after the procedure. The child, parent and nurse were blinded to each other's assessments. In addition, parents were asked to report their own distress during their child's needle insertion on a VAS.

In addition to the VAS assessments, behavioural observation of the child's pain was made using the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS).[21] A nurse not involved in the needle procedure, who had received training in behavioural observations, made the observation with focus on the first minute after the needle insertion. CHEOPS was originally developed to measure postoperative pain in children and is today considered a well-established measure of brief paediatric pain episodes.[20] The maximum CHEOPS score is 13, and the minimum score is four. A score ≥7 is considered to indicate pain during procedures.[17,21,22]

The procedure time was measured from intake of medication to completion of the procedure, that is, when the needle was in place. Cortisol in serum was sampled at the time of the needle insertion (baseline) and after 30 minutes (through the existing needle in the port in both instances).

2.7 | Sample size

For this feasibility and pilot study, a number of approximately 20 were deemed sufficient. For the planned RCT, previous studies have suggested that a change of 13-18 mm for pain on a VAS indicates a clinically relevant difference.[23-26] In accordance with this, we decided to interpret a difference of 15 mm as relevant for the variables pain, fear and distress. With a standard deviation of 20 mm found in previous studies,[4-7,26] we calculated that we would need 25 children in each group to get a power of 0.8 with an alpha value of 0.05. The intervention needed to be piloted, and we decided that if the feasibility criteria were met and if we found that logistics of administering the intervention were practical and without a need to change, we could use the pilot results in the main RCT as an internal pilot.[27] In the pilot sample with 11 in one group and 12 in the other, we only reached a power of 0.54 with an alpha of 0.05 with a one-tailed test, which must be kept in mind discussing effect trends. We used a one-tailed test in this calculation because our hypothesis implicated direction; that is that ibuprofen would be superior to placebo.

2.8 | Statistical analysis

Feasibility data and effect trend data are reported with descriptive statistics. The data have been analysed and reported according to the CONSORT guidelines and intention to treat. There were no deviations from randomised allocation. Chi-square test was used to investigate potential differences between sexes and physical status between the ibuprofen and placebo group. Independent *t* test was used to investigate whether there were any differences between the groups with regard to (a) age, weight, height, time since diagnosis and time since last needle procedure and (b) pain, fear, distress, CHEOPS, procedure time and cortisol reduction. The use of parametric statistics in the analysis of VAS data can be challenged. In addition to the parametric tests, we performed non-parametric tests (Mann-Whitney *U* test). The results from the non-parametric tests were consistent with the results of the parametric tests in all analyses. The statistical analyses were performed using IBM SPSS 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Mac, Version 20.0). The alpha value was set at 0.05.

3 | RESULTS

3.1 | Participant flow

Of 29 eligible children, 23 (79%) agreed to participate in the study (Figure 1). Reasons for not participating included the following: The child would not take mixtures per os, unwillingness to take extra medications and psychological factors.

Diagnoses represented were leukaemia (n = 15), brain tumours (n = 5) and other solid tumours (n = 3). Participants' characteristics are presented in Table 1. There were no differences between the ibuprofen (IG n = 12) and placebo group (PG n = 11) with respect to age, gender, weight, height, physical status, weeks after diagnosis or weeks after last needle insertion.

3.2 | Recruitment, retention and data collection

The criteria for feasibility success and effect trends are presented in Table 2.

During the study time, fewer children than expected were eligible for inclusion in the study; hence, the inclusion criterion for feasibility was not met. Many children met one or more exclusion criteria. The most common reason for exclusion was interacting medications and a need for immediate needle insertion. Missing data consisted of two CHEOPS observations (IG = 0, PG = 2), and for one child in the IG, a parent was not present in the room during the needle procedure resulting in missing values for parents VAS scores. This resulted in 2% missing data in total. S-cortisol samples were taken from 21 children (91%).

3.3 | Trends of treatment effect

The mean VAS (SD) for distress for oral intake of the drug in the IG was 10.6 (14.7.) according to parents, 6.3 (6.7) according to nurses and 11.2 (11.3) according to children (>7 years of age). In the PG, distress at oral intake was 11.1 (20.1) according to parents, 11.9 (10.6) according to nurses and 29.5 (35.5) according to children. The child's pain, fear and distress at needle insertion according to children, parents and nurses are presented in Table 3. Mean VAS score (SD) for parents own fear in the IG was 1.2 (1.3) and in the PG 17.6 (21.3), $P < .01$.

Mean (SD) CHEOPS score in the IG was 9.8 (3.1) and in the PG 7.4 (2.6).

Four children (≥7 years old) thought that the medication was beneficial (IG = 2, PG = 2). Of the parents and nurses, the corresponding numbers were 10 parents (IG = 5, PG = 5) and 19 nurses (IG = 9, PG = 10).

Procedure time for the IG was 1:10 hours (SD 0:11) and for the PG 1:04 hours (SD 0:05). Mean cortisol reduction in the IG (n = 12) was 21.7 (SD 86.5) and in the PG (n = 7) 7.2 (SD 90.9), $P = .7$.

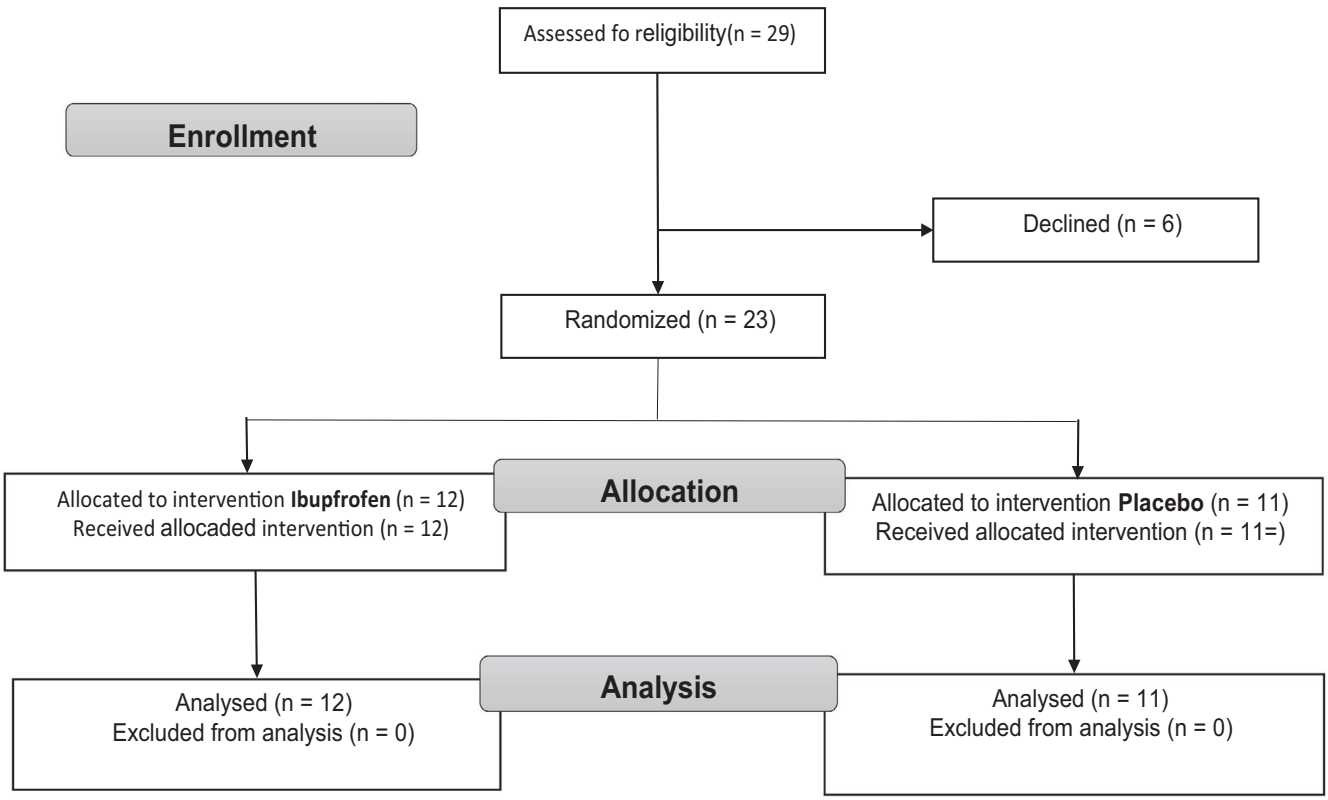

FIGURE 1 Flow diagram of the participants

TABLE 1 Patients and dose characteristics

	Ibuprofen	Placebo
n	12	11
Age, years, mean (SD)	10.6 (6.0)	7.8 (6.2)
<7/≥ 7 y	6/6	5/6
Girl/Boy	6/6	4/7
Weight (kg), mean (SD)	37.5 (23.7)	35.6 (26.4)
Length (cm), mean (SD)	143.0 (34.8)	126.4 (37.9)
Physical status ASA I/II/III	1/8/0 (missing 3 = 0)	1/7/0 (missing = 0)
Weeks from diagnosis, mean (SD)	51.7 (52.0)	31.4 (33.9)
Weeks from latest needle insertion, mean (SD)	2.2 (1.8)	2.3 (2.4)
Dose (mg/kg)	7.0 (0.7)	7.0 (1.0)

Note: Children in ASA group 1 had finished their treatment.
Abbreviation: ASA, American Society of Anesthesiologists' Physical Status Classification System.

No serious side effects were observed nor reported. One child in the IG and two in the PG reported distress due to bad taste of the medication.

4 | DISCUSSION

In this feasibility and pilot study testing ibuprofen in a needle procedure, recruitment of participants was more difficult than expected mainly due to frequently met exclusion criteria. Hence, the predefined feasibility criteria were not reached. Parents, nurses and children reported no trend of benefit of oral ibuprofen at a dose of 7.5 mg/kg body weight with regard to pain, fear and distress compared with placebo. All children included followed the study protocol and were able to take the oral solution of Ibuprofen with little discomfort reported. The amount of missing data was low, and serum-cortisol values were taken from >90% of the participants which indicates that the study was well implemented at the clinic but the low recruitment and lack of effect did not motivate the RCT to proceed.

Ibuprofen is commonly used in paediatric practice. However, many children with cancer receive treatments that interact with ibuprofen and during times of thrombocytopenia, which is common, the use of NSAIDs is not appropriate. Given these facts, it might have been better to include children without malignant diseases. However, the study was one part of a number of studies investigating procedural pain, specifically during needle procedures, in a paediatric oncology setting and it was considered to be of interest to investigate if ibuprofen might prove helpful. Also, it was considered valuable to undertake the study at a ward already familiar with the procedures. In addition, when coming to have a needle inserted for chemotherapy, the children in general have normalised thrombocyte counts.

Regarding the trends of effect, the study shows the same pattern, with fear and distress being as troublesome as pain during needle insertions in children, as in previous studies.[4-7] This might be explained by the use of topical anaesthesia that alleviates the pain during needle insertion. Ibuprofen has no known anxiolytic or sedative effect, and we would not expect that it would have an effect on fear. However, since this was part of a series of similar studies, we wanted to use the same methods for evaluation and also wanted to control for this information. Parents of children who received ibuprofen rated their own fear during the needle procedure lower than parents of children receiving placebo. With the small number of observations, it is not possible to draw any conclusions about the meaning of this difference. Parents, nurses and children receiving either ibuprofen or placebo thought the treatment were equally beneficial. From the child perspective, it could be argued that, even though the risk of side effects of ibuprofen is very low in this setting, it would be preferable to always start with non-pharmacological

TABLE 2 Feasibility criteria and results

Variable	Criteria for success	Results	Criteria reached
Recruitment	4 children/mo	1.44/mo	No
Consent rate	80% of children/parents asked to participate agreed	79%	No
Compliance	90% of children included completed planned treatment	100%	Yes
Data collection	No more than 5% missing data in total	2%	Yes
Blood samples	S-cortisol samples analysed in 90% of children	91%	Yes

TABLE 3 Childrens pain, fear and distress at needle insertion according to nurses', parents' and childrens' (≥7 y) reports[a]

	Ibuprofen				Placebo				
	n	Mean	Median	SD	n	Mean	Median	SD	*P*
Nurses									
Fear	12	37.3	20.0	37.4	11	27.5	17.0	25.4	n.s
Distress	12	39.7	29.5	35.3	11	22.6	11.0	23.9	n.s
Pain	12	23.3	11.5	25.2	11	17.3	7.0	24.8	n.s
Parents									
Fear	11	33.9	25.0	34.2	11	19.8	15.0	23.6	n.s
Distress	11	29.5	19.5	29.5	11	30.1	15.0	32.8	n.s.
Pain	11	14.1	13.0	12.3	11	24.8	9.0	29.6	n.s
Children									
Fear	6	6.7	2.5	8.7	6	5.8	3.5	6.4	n.s
Distress	6	10.8	5.0	14.5	6	15.2	4.5	20.0	n.s
Pain	6	13.2	9.5	16.0	6	13.5	4.5	17.9	n.s

[a]Responses to questions answered on a 100 mm VAS with anchors at the extreme ends.

interventions. It is generally agreed that patients are the best raters of their experiences, and self-report is the gold standard.[28] Our decision to also assess children's pain, fear, and distress according to parents as well as nurses was based on the assumption that various informants may identify different aspects of a phenomenon as suggested by others.[29,30]

The strengths of this study are the randomised double-blind placebo-controlled design and that there were no differences between the two groups regarding age, gender, diagnosis, time since last needle insertion and amount of missing data. We included children from 1 year of age. From an ethical point of view, it is important not to exclude the youngest children from pharmacological studies. The stratification of children </> 7 years made it possible to collect self-reported data from the older children, and even though only 12 children ≥7 years old were included, this information adds important value to the study. Limitations of the study are the low recruitment rate resulting in the small number of children included and the diversity of ages and diagnoses. Another limitation is that the administered dose of ibuprofen was relatively low. At the time of the study, the recommended dose was 5.0-7.5 mg/kg and presently it is 7.5-10.0 mg/kg with 10 mg/kg given as a loading dose. Furthermore, today, we would have tried to include also non-Swedish speaking children. Reasons not to include them at the time were that information and consent forms and questionnaires were only available in Swedish. From this study, we cannot see any trends that ibuprofen has a beneficial effect during needle insertions in children and given that other studies have shown good effect of distraction[4] and midazolam[5] and that pain was not considered the biggest problem for the children, it was not considered reasonable to continue with the study.

5 | CONCLUSIONS

The study failed to meet the feasibility criteria and was closed due to low recruitment rate and absence of trend of effect of oral ibuprofen on experienced pain, fear and distress among children undergoing needle insertion into a subcutaneously implanted intravenous port. From this data, we cannot state that ibuprofen is not helpful in needle procedures but that it seems unlikely. Considering the lack of data in this area in the literature, we think that this study adds information that will be valuable for planning future research in the area.

ACKNOWLEDGEMENTS

The authors would like to thank the staff for technical and material support.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

ETHICAL APPROVAL

The study was approved by the Regional Ethical Committee 2004:M-362 and by the Medical Product Agency. Written consent for participation and an agreement for data to be stored and processed only for research purposes were obtained from participants and their parents/guardians.

ORCID

Tove Kamsvåg https://orcid.org/0000-0003-2696-4054

REFERENCES

1. Ljungman G, Gordh T, Sorensen S, Kreuger A. Pain variations during cancer treatment in children: a descriptive survey. *Pediatr Hematol Oncol*. 2000;17(3):211-221.
2. Ljungman G, Kreuger A, Gordh T, Berg T, Sorensen S, Rawal N. Treatment of pain in pediatric oncology: a Swedish nationwide survey. *Pain*. 1996;68(2–3):385-394.
3. Ali S, Chambers A, Johnson DW, et al. Reported practice variation in pediatric pain management: a survey of Canadian pediatric emergency physicians. *CJEM*. 2013;15:1-9.

4. Heden L, von Essen L, Ljungman G. Randomized interventions for needle procedures in children with cancer. *Eur J Cancer Care*. 2009;18(4):358-363.
5. Heden L, von Essen L, Frykholm P, Ljungman G. Low-dose oral midazolam reduces fear and distress during needle procedures in children with cancer. *Pediatr Blood Cancer*. 2009;53(7):1200-1204.
6. Heden L, von Essen L, Ljungman G. Effect of high-dose paracetamol on needle procedures in children with cancer - a RCT. *Acta Paediatr*. 2014;103(3):314-319.
7. Heden LE, von Essen L, Ljungman G. Effect of morphine in needle procedures in children with cancer. *Eur J Pain*. 2011;15(10):1056-1060.
8. Litalien C, Jacqz-Aigrain E. Risks and benefits of nonsteroidal anti-inflammatory drugs in children: a comparison with paracetamol. *Paediatr Drugs*. 2001;3(11):817-858.
9. Ong CK, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. *Anesth Analg*. 2010;110(4):1170-1179.
10. Mehlisch DR, Aspley S, Daniels SE, Southerden KA, Christensen KS. A single-tablet fixed-dose combination of racemic ibuprofen/paracetamol in the management of moderate to severe postoperative dental pain in adult and adolescent patients: a multicenter, two-stage, randomized, double-blind, parallel-group, placebo-controlled, factorial study. *Clin Ther*. 2010;32(6):1033-1049.
11. Southworth S, Peters J, Rock A, Pavliv L. A multicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen 400 and 800 mg every 6 hours in the management of postoperative pain. *Clin Ther*. 2009;31(9):1922-1935.
12. Viitanen H, Tuominen N, Vaaraniemi H, Nikanne E, Annila P. Analgesic efficacy of rectal acetaminophen and ibuprofen alone or in combination for paediatric day-case adenoidectomy. *Br J Anaesth*. 2003;91(3):363-367.
13. Pickering AE, Bridge HS, Nolan J, Stoddart PA. Double-blind, placebo-controlled analgesic study of ibuprofen or rofecoxib in combination with paracetamol for tonsillectomy in children. *Br J Anaesth*. 2002;88(1):72-77.
14. Perrott DA, Piira T, Goodenough B, Champion GD. Efficacy and safety of acetaminophen vs ibuprofen for treating children's pain or fever: a meta-analysis. *Arch Pediatr Adolesc Med*. 2004;158(6):521-526.
15. Makela AL, Lempiainen M, Ylijoki H. Ibuprofen levels in serum and synovial fluid. *Scand J Rheumatol Suppl*. 1981;39:15-17.
16. FASS. http://fass.se. cited 200401
17. McGrath PJ, Stevens BJ, Walker SM, Zempsky WT. *Oxford Textbook of Paediatric Pain*. Oxford: Oxford University Press; 2014.
18. Felt BT, Mollen E, Diaz S, et al. Behavioral interventions reduce infant distress at immunization. *Arch Pediatr Adolesc Med*. 2000;154(7):719-724.
19. Hanrahan K, McCarthy AM, Kleiber C, Lutgendorf S, Tsalikian E. Strategies for salivary cortisol collection and analysis in research with children. *Appl Nurs Res*. 2006;19(2):95-101.
20. McGrath PJ, Walco GA, Turk DC, et al. Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. *J Pain*. 2008;9(9):771-783.
21. McGrath PJ, Goodman G, Dunn JT, Chapman J. CHEOPS: A behavioral scale for rating postoperative pain in children. In: Fields HLDR, Cervero F, eds. *Advances in Pain Research and Therapy*, 9th edn. New York, NY: Raven Press; 1985:395-402.
22. von Baeyer CL, Spagrud LJ. Systematic review of observational (behavioral) measures of pain for children and adolescents aged 3 to 18 years. *Pain*. 2007;127(1–2):140-150.
23. Hee HI, Goy RW, Ng AS. Effective reduction of anxiety and pain during venous cannulation in children: a comparison of analgesic efficacy conferred by nitrous oxide, EMLA and combination. *Paediatr Anaesth*. 2003;13(3):210-216.
24. Todd KH, Funk JP. The minimum clinically important difference in physician-assigned visual analog pain scores. *Academic Emerg Med*. 1996;3(2):142-146.
25. Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. *Ann Emerg Med*. 1996;27(4):485-489.
26. Bishai R, Taddio A, Bar-Oz B, Freedman MH, Koren G. Relative efficacy of amethocaine gel and lidocaine-prilocaine cream for Port-a-Cath puncture in children. *Pediatrics*. 1999;104(3):e31.
27. Arain M, Campbell MJ, Cooper CL, Lancaster GA. What is a pilot or feasibility study? A review of current practice and editorial policy. *BMC Medi Res Methodol*. 2010;10:67.
28. Finley GA, McGrath PJ. *Measurement of Pain in Infants and Children*. Seattle, WA: IASP Press; 1998.
29. Manne SL, Jacobsen PB, Redd WH. Assessment of acute pediatric pain: do child self-report, parent ratings, and nurse ratings measure the same phenomenon? *Pain*. 1992;48:45-52.
30. Berde C, Wolfe J. Pain, anxiety, distress, and suffering: Interrelated, but not interchangeable. *J Pediatr*. 2003;142:361-363.

How to cite this article: Kamsvåg T, Hedén L, von Essesn L, Ljungman G. Ibuprofen in needle procedures in children with cancer—A feasibility and pilot study. *Acta Paediatr*. 2020;00:1–7. https://doi.org/10.1111/apa.15449