

Comparison of the Efficacy of Homeopathic Drug *Arnica* and Ibuprofen on Postextraction Pain in Children: A Triple-blind Randomized Controlled Trial

Jagruti H Thakur¹, Amar N Katre²

ABSTRACT

Aim: To compare the homeopathic drug *Arnica* with ibuprofen as an analgesic for postextraction pain control in children.

Materials and methods: Forty-four healthy children between 8 and 12 years of age requiring two clinical sessions of tooth extraction in two different quadrants of the oral cavity were selected for the study. All the children received both the drugs in this crossover trial with a washout of 10 days. Patient-rated and operator-assessed pain was compared to a 10-point validated Visual Analog Scale at baseline, 24, 48, and 72 hours using the paired t-test. Acceptance to taste and frequency of dosing was recorded at the end of three days using a five-point Likert scale and were compared using the Chi-squared test. Kappa statistics were performed to assess intraoperator variability.

Results: Pain reduction by Ibuprofen was significantly more than *Arnica* only at 48 hours with respect to both patient-reported and operator-assessed pain [(t = 3.567, p < 0.05), (t = 2.834, p < 0.05)]. As the age of the child increased, patient-reported pain significantly decreased. Children preferred the taste of *Arnica* over that of Ibuprofen ($\chi^2 = 56.76, p < 0.0001$).

Conclusion: There was no difference between *Arnica* and Ibuprofen in the postextraction pain management in 8–12-year-old children.

Clinical significance: The results of this study suggest that *Arnica* may be considered as an alternative to ibuprofen in managing postextraction pain in 8–12-year-old children, especially those with asthma, COPD, or known allergy to ibuprofen.

Keywords: *Arnica*, Children, Ibuprofen, Postextraction pain.

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INTRODUCTION

Dental pain may be associated with disorders of the oral cavity or with dental procedures intended to cure them.¹ Pain not only signals tissue injury, but it also acts as an impediment to most dental procedures, delays the resumption of normal activities following dental surgical procedures, and lessens the likelihood of patients seeking dental procedures in the future.² Tooth extraction is the most likely pediatric dental procedure to produce inflammation and pain. Previous studies report that some children experienced postextraction pain severe enough to require analgesics for relief.^{3,4} Optimal analgesic therapy for ambulatory dental patients should be efficacious and should lessen the prospects for pain associated with dental therapy.

NSAIDs have been successfully employed in clinical dental practice for postoperative pain management.^{5,6} Ibuprofen appears comparable to other non-steroidal anti-inflammatory drugs when evaluated in the oral surgery model and is routinely used and deemed safe in pediatric dental practice.⁷ It is, however, contraindicated in patients with asthma and COPD.^{8,9} With the increasing burden of asthma,¹⁰ it is important to find an alternative to ibuprofen.

Homeopathy, as an alternative branch of medicine, has been steadily growing worldwide.^{11,12} *Arnica* has been used in cases of bruises and inflammation for pain management and healing of wounds.¹³ Many homeopathic medications such as Belladonna, Chamomilla, Coffea Cruda, Hepar sulph, *Arnica*, and Plantago have been used in dentistry.¹⁴ *Arnica* and *Hypericum* have been used for pain management in dentistry.¹⁵

The plant *Arnica montana*, when ingested, can induce vascular dilation, blood stasis, and increased capillary permeability.¹³

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This plant can induce muscular pain and rigidity similar to the accumulation and crystallization of lactic acid after excessive physical exercise. Based on the law of homeopathy "Similia Similibus Curantur,"¹⁶ by producing symptoms similar to those experienced during and after extraction, *Arnica* may prepare the body to deal with the postextraction pain.

Arnica is a safe analgesic in asthmatics.¹³ There are a few studies advocating the use of *Arnica* in dental procedures,^{13,17} but none in children, necessitating its further clinical evaluation. Hence, a study was conducted with the aim to compare *Arnica* with ibuprofen as an analgesic for post-extraction pain control in children at 24, 48, and 72 hours.

MATERIALS AND METHODS

Population and Settings

The CONSORT checklist was followed to report this 2*2 crossover randomized trial.

The study commenced after obtaining Ethical approval from the Institutional Ethics Committee. The study was conducted in the Department of Pedodontics and Preventive Dentistry, YMT Dental College, Navi Mumbai (an urban locality), India. Eight–12-year-old children who visited the department for dental treatments from December 2016 to February 2017 were the subjects for the study.

Otherwise healthy children with teeth indicated for extraction in two different quadrants of the oral cavity with grade I or lesser mobility were recruited for the study.

Children suffering from any systemic condition that may limit the use of ibuprofen or *Arnica* especially COPD or respiratory diseases, children with a known hypersensitivity to ibuprofen or other NSAIDs were excluded from the study. Other exclusion criteria were acute infections in the orofacial region to be treated, children with greater than one-half root resorption, children on any other anti-inflammatory medications, or those who did not cooperate while performing the procedure.

Interventions

All children received both the drugs, that is., 200C *Arnica* Montana (labeled A) and ibuprofen (labeled B). Both the drugs were packaged in powdered forms with Saccharum lactum as the vehicle by an independent observer. Both the drugs were dispensed in equally weighted, similar-sized, identical-looking white packets to ensure blinding for the operator and the participant. Two clinical sessions of a tooth extraction with a wash-out period of 10 days between them were conducted to enable crossover. Escape medication in form of paracetamol was provided to all patients.

Arnica was administered 30 minutes prior to the extraction procedure (in accordance with the homeopathic drug administration protocols), children in the ibuprofen group received only Saccharum lactum in the preoperative dose, these were marked as 1 on the packets. Postextraction, both the drugs were administered three times a day with an interval of 8 hours between two doses. Drug dosage for ibuprofen was calculated according to patients' weight and that for *Arnica* was standardized as per the homeopathic dosage recommendations.

Before the extraction, the local anesthesia procedure and the use of the Visual Analog Scale were explained to the patient using euphemisms and a Tell-show-do technique, respectively. Local anesthesia was delivered using site-appropriate techniques as described by Malamed.¹⁸

Variables

Patient-rated and operator-assessed pain was recorded on a 10-point VAS. Patient-rated pain was recorded at baseline, 24, 48, and 72 hours. Operator-assessed pain was recorded by palpating at the site of extraction with the index finger at baseline, 24, 48, and 72 hours using the same scale. The effect of the period (sequence of drug administration) on patient response was also assessed.

Acceptance to taste and frequency of dosing was recorded at the end of three days using a five-point Likert scale.

The need for escape medication and adverse effects of both the drugs were also recorded.

Sample Size Estimation

Based on the previous literature¹⁹ and in the absence of literature comparing *Arnica* and ibuprofen in children, a noninferiority margin hypothesis has been proposed for this study.

The sample size estimation was based on the primary outcome variable, that is, VAS for pain over 4 days of therapy with *Arnica* Montana after dental extraction. In a previous study,¹⁹ the reported mean pain scores were recorded on a 0–100 VAS. However, with a 0–10 VAS used in the present study to detect an estimated difference of 5 with β adjusted at 0.1937 and α at 0.05, with four repeated measurements, a total of 36 children would be necessary to detect noninferiority assuming a randomized 2 x 2 crossover design with an equal number in each sequence. Assuming a 20% dropout rate of patients due to non compliance, or other factors, 44 patients were enrolled in the study.

The allocation to the two groups was carried out by a table of random numbers drawn online (<http://www.randomization.com>, seed- 16,455) and a 1:1 allocation ratio was maintained.

Statistical Plan

The self-reported and operator assessed pain (VAS) scores were represented as means and were compared at different time intervals (baseline, 24, 48, 72 hours) using a paired *t*-test. A repeat measures analysis of variance (ANOVA) was employed to determine the effect of the period on pain scores. Acceptance to taste and the frequency of dosing were represented as proportions and were assessed using a chi-squared test. The effect of gender and age were analyzed using the Analysis of Covariance (ANCOVA). Kappa statistics were employed to assess intra-examiner variability for pain rating.

RESULTS

The sample consisted of 44 children out of which 52.27% were boys. About 75% of the children belonged to the 8–10 years age-group. The drop-out rate was 4.54%. A total of 42 participants completed both sessions (Flowchart 1). Nearly 52.38% of participants received *Arnica* first, and 47.62% of participants received ibuprofen first. About 78.57% of participants underwent single tooth extraction. Around 52.4% of the teeth extracted were in the mandibular arch (Table 1).

There was no statistically significant difference between the baseline pain scores for both categories ($F = 0.656, p > 0.05$). Overall, no difference was noted in the pain scores for *Arnica* and ibuprofen. On the parameter of patient-reported pain, the pain reduction by ibuprofen at the end of 48 hours was statistically more significant than *Arnica* [($t = 3.567, p < 0.05$), ($F = 12.73, p < 0.05$)]. On the parameter of operator assessed pain, the pain reduction by ibuprofen at the end of 48 hours was statistically more significant than *Arnica* [($t = 2.834, p < 0.05$), ($F = 8.034, p < 0.05$)]. The period did not have a significant effect on patients' response to the two drugs at any time interval (Tables 2 and 3).

The mean patient-reported pain score and operator-assessed pain score with age as a covariable were 9.4881 ± 1.3405 [$(F = 0.280, p > 0.05)$] and 9.4881 ± 1.3405 [$(F = 5.643, p < 0.05)$], respectively. The operator-assessed pain scores were significantly affected by age. As age increased, the pain reported decreased. Gender had no significant effect on patient-reported and operator-assessed pain scores [($F = 1.854, p > 0.05$)] [($F = 3.845, p > 0.05$)] (Table 4).

Children preferred the taste of *Arnica* over that of ibuprofen and this difference was statistically significant ($\chi^2 = 56.76, p < 0.0001$) (Table 5). There was no statistically significant difference

Flowchart 1: CONSORT flow diagram

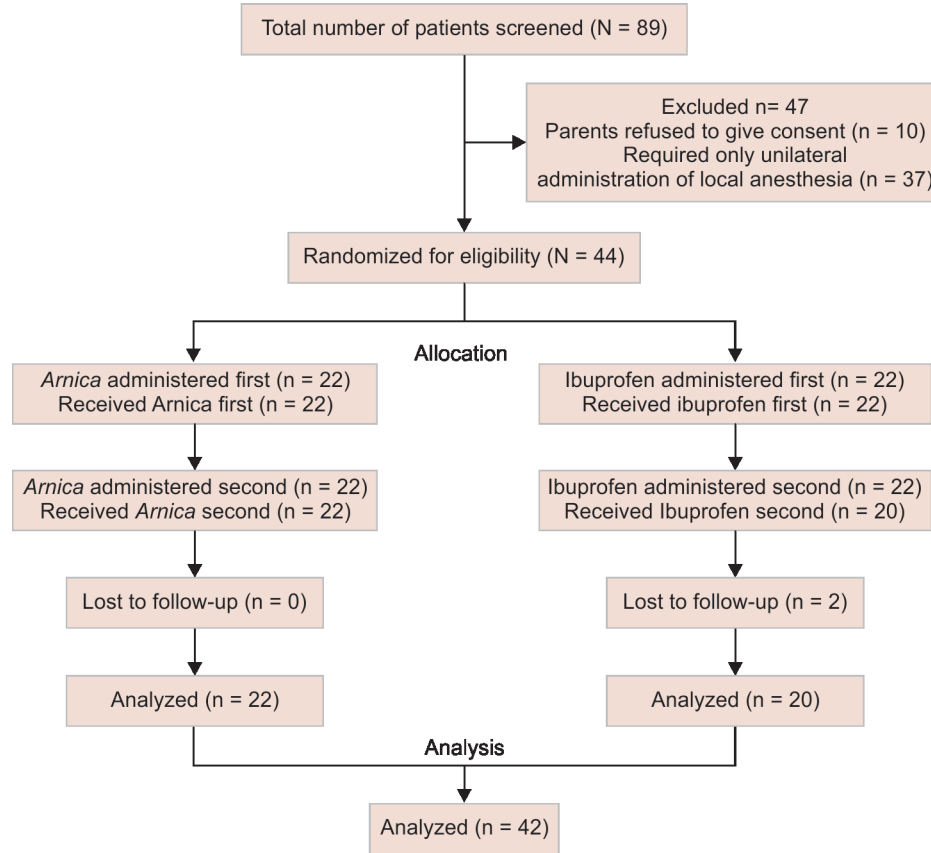


Table 1: Distribution of the study population

| Participants | Age | | No. of teeth extracted* | | Arch* | | First drug* | |
|----------------|------------|--------------|-------------------------|-----------|------------|------------|-------------|------------|
| | 8–10 years | >10–12 years | 1 tooth | 2 teeth | Maxilla | Mandible | Arnica | Ibuprofen |
| Boys (n = 23) | 18 (40.9%) | 5 (11.4%) | 18 (42.9%) | 5 (11.9%) | 7 (16.6%) | 16 (38.1%) | 10 (23.8%) | 13 (31%) |
| Girls (n = 21) | 15 (34.1%) | 6 (13.6%) | 15 (35.7%) | 4 (9.5%) | 13 (31%) | 6 (14.3%) | 12 (28.6%) | 7 (16.6%) |
| Total (N = 44) | 33 (75%) | 11 (25%) | 33 (78.6%) | 9 (21.4%) | 20 (47.6%) | 22 (52.4%) | 22 (52.4%) | 20 (47.6%) |

*N = 42

Table 2: Comparison of patient-reported pain (VAS) score between *Arnica* and Ibuprofen with period as a variable

| | <i>Arnica</i> | | <i>Ibuprofen</i> | | Tests of significance | | | |
|--------|---------------|----------------------------|------------------|----------------------------|-----------------------|---------|---|--|
| | Mean ± SD | Adjusted mean [#] | Mean ± SD | Adjusted mean [#] | t test | | ANOVA | |
| | | | | | t | p | F | p |
| B | 0.214 ± 0.812 | 0.3500 [#] | 0.405 ± 1.289 | 0.4500 [#] | -0.810 | 0.420 | 0.656 ^a 0.132 [#] | 0.420 ^a 0.717 [#] |
| 24 hrs | 2.809 ± 2.167 | 3.2500 [#] | 2.524 ± 2.431 | 3.1000 [#] | 0.568 | 0.571 | 0.323 ^a 0.0678 [#] | 0.571 ^a 0.795 [#] |
| 48 hrs | 2.214 ± 2.089 | 2.4500 [#] | 0.786 ± 1.538 | 1.2500 [#] | 3.567 | 0.0006* | 12.73 ^a 0.300 [#] | <0.001 ^{a*} 0.585 [#] |
| 72 hrs | 0.619 ± 1.884 | 0.7000 [#] | 0.404 ± 1.268 | 0.3000 [#] | 2.168 | 0.4269 | 4.702 ^a 0.108 [#] | 0.033 ^{a*} 0.743 [#] |

N = 42; [#]Period as a variable assessed using two - way ANOVA; ^aRepeat measures ANOVA; (*p < 0.05- significant); SD, standard deviation



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Table 3: Comparison of operator-assessed pain (VAS) score between *Arnica* and Ibuprofen with period as a variable

| | <i>Arnica</i> | | <i>Ibuprofen</i> | | Tests of significance | | | |
|--------|---------------|----------------|------------------|----------------|-----------------------|---------|------------------------------|-------------------------------|
| | Mean ± SD | Adjusted mean# | Mean ± SD | Adjusted mean# | t-test | | ANOVA | |
| | | | | | T | p | F | p |
| B | 0.286 ± 1.065 | 0.4000# | 0.262 ± 0.938 | 0.3000# | 0.109 | 0.9137 | 0.012 ^a 0.108# | 0.914 ^a 0.743# |
| 24 hrs | 3.214 ± 2.64 | 3.4500# | 2.881 ± 2.587 | 3.3000# | 0.582 | 0.5624 | 0.338 ^a 0.092# | 0.562 ^a 0.762# |
| 48 hrs | 2.642 ± 2.730 | 2.6000# | 1.190 ± 1.890 | 1.8000# | 2.834 | 0.0058* | 8.034 ^a 1.485# | 0.006 ^{a*} 0.227# |
| 72 hrs | 1.047 ± 1.752 | 0.8000# | 0.404 ± 1.269 | 0.7000# | 1.925 | 0.0577 | 3.706 ^a 2.415# | 0.058 ^a 0.124# |

N = 42; # Period as a variable assessed using two - way ANOVA; ^a Repeat measures ANOVA; (*p < 0.05- significant); SD, standard deviation

Table 4: Comparison of pain (VAS) score between *Arnica* and Ibuprofen with age and gender as a covariable

| | Gender | | Age | |
|---------------|---------------|-------------------|---------------|-------------------|
| | Self-reported | Operator-assessed | Self-reported | Operator-assessed |
| Adjusted mean | 0.9643 | 1.1845 | 9.4881 | 9.4881 |
| F | 1.854 | 3.845 | 0.280 | 5.643 |
| p | 0.174 | 0.051 | 0.597 | 0.018 |

(*p < 0.05- significant) (p > 0.05- not significant)

Table 5: Comparison of acceptance to taste between *Arnica* and Ibuprofen

| Drug | Likert scale# | | | | | χ ² | p |
|---------------|---------------|-----------|-------------|-------------|---|----------------|---------|
| | 1 | 2 | 3 | 4 | 5 | | |
| <i>Arnica</i> | 36 85.7% | 0 0.0% | 4 9.5% | 2 4.8% | 0 | 56.76 | <0.0001 |
| Ibuprofen | 2 4.8% | 1 2.4% | 13 31.0% | 26 61.9% | 0 | | |
| Total | 38 (45.2%) | 1(1.2%) | 17(20.2%) | 28(33.3%) | 0 | | |

#1- Liked very much, 2- Liked, 3- Neither liked nor disliked, 4- Didn't like, 5- Didn't like at all

in the acceptance to the frequency of dosage of two drugs amongst children ($\chi^2 = 1.384, p > 0.05$).

The kappa score for intraexaminer reliability for operator-assessed pain was 0.628. None of the patients required the escape medication. No adverse effects were reported with the usage of either of the drugs.

DISCUSSION

Asthma is one of the commonest ailments affecting children.^{10,20} ibuprofen has been successfully employed in clinical dental practice for postoperative pain management. It is, however, contraindicated in patients with asthma and COPD,⁸ hence the need for an alternative analgesic.

Homeopathy as an alternative branch of medicine has been steadily growing in India and *Arnica* and *Hypericum* has been used as the most common agents for pain management.^{13,15} Pain associated with dental extraction is due to inflammation and hence *Arnica* is better-suited postextraction than *Hypericum*.²¹

Pain may be regarded as the proxy measure for inflammation following dental extraction. Studying postsurgical dental pain is a sensitive method for evaluating analgesic drugs. Postextraction dental pain model has been widely used to compare various

analgesics.²² Hence, this model was employed in the present study to compare the analgesic efficacy of the two drugs. Pain is a qualitative and subjective emotion experienced by the patient. Pain is better elicited at 7 years and above²³ hence, children aged 8–12 years were recruited for the study.

A validated, self-reported pain scale (Visual Analog Scale) was used in this study to assess self-reported and operator-assessed pain postextraction. The VAS has been shown to have good validity and sensitivity in patients aged seven and above.²³ The pain threshold is also different for every patient. Therefore, an additional variable of operator assessed pain elicited at the site of extraction was recorded by palpating the area of extraction.

Acceptable palatability is paramount for pediatric formulations. Most active pharmaceutical ingredients (APIs) are highly bitter and this is the main difficulty behind the palatable preparation for pediatric therapy.²⁴ Children's acceptance of the taste of the drugs was hence noted on a five-point Likert scale.

Overall, no difference was noted in the pain scores for *Arnica* and ibuprofen. *Arnica* was found to be as efficacious as ibuprofen in alleviating postextraction pain in 8–12-year-old children. This is in accordance with the previous study reported in literature where *Arnica* was found to be comparable to NSAIDs in adult patients.²⁵

In a previous study reported by Macedo et al.,¹⁷ *Arnica* was significantly better in reducing pain and edema as compared to placebo. *Arnica* has been effectively used for controlling inflammation-based pain situations in previous studies on the extraction of third molars in adults. On the parameter of self-reported and operator assessed pain ibuprofen was reported to be better at the end of 48 hours. This could be because ibuprofen suppresses inflammation over the 2–3-day postoperative course when edema formation associated with the inflammatory process is most prominent.²⁶ Period as a covariable had no significant difference indicating that the sequence of drug administration has no influence on patients' response to pain.

No previous study reports operator-assessed pain as a parameter.

Children preferred the taste of *Arnica* over ibuprofen and this was statistically significant. The sensory systems in children mature postnatally and their responses to certain tastes differ markedly from adults. Amongst these differences are heightened preferences for sweet-tasting and greater rejection of bitter-tasting foods.²⁷ The effect of individual taste preferences was not considered.

Limitations

The VAS scale for measuring pain perception may not portray all the characteristics of pain response. However, we selected this measure as it is easy for the child participants to understand and rate and is the most widely used in similar studies in the recent literature.²⁸ Baseline anxiety and its effect on pain response which could have affected the procedure were not addressed and could not be studied independently. In absence of prior literature comparing the two drugs for pain management postextraction and a differently calibrated scale, we had to estimate the mean difference. This difference may not have been represented through this sample. The results of this study may be generalizable to children of similar age groups in similar study settings.

CONCLUSION

We concluded that there was no difference between *Arnica* and ibuprofen in the postextraction pain management in 8–12-year-old children. The sequence of drug administration had no crossover effect on the patients' responses to pain. The taste of *Arnica* was preferred by children as compared to that of ibuprofen. There was no difference in the acceptance to the frequency of dosage between *Arnica* and ibuprofen.

CLINICAL SIGNIFICANCE

- *Arnica* may be considered as an alternative to ibuprofen in managing postextraction pain in 8–12-year-old children, especially those with asthma or COPD or known allergy to ibuprofen.
- Different homeopathic formulations could be compared with various NSAIDs for other age-groups.

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REFERENCES

1. Da Costa RSM, Ribeiro SN, Cabral E. Determinants of painful experience during dental treatment. *Rev Dor São Paulo* 2012;13(4):365–370.
2. Gordon SM, Dionne RA. Prevention of pain. *Comp Cont Edu Dent* 1997;18(3):239–242.
3. Acs G, Moore PA, Needleman HL et al. The incidence of post-extraction pain and analgesic usage in children. *Anesth Prog* 1986;33(3):147–151.
4. Primosch RE, Nichols DL, Courts FJ. Comparison of preoperative ibuprofen, acetaminophen, and placebo administration on the parental report of postextraction pain in children. *Pediatr Dent* 1995;17(3):187–191.
5. Dionne RA, Cooper SA. Evaluation of preoperative ibuprofen for postoperative pain after removal of third molars. *Oral Surg Oral Med Oral Pathol* 1978;45(6):851–856. DOI: 10.1016/s0030-4220(78)80004-8
6. Pierce CA, Voss B. Efficacy and safety of ibuprofen and acetaminophen in children and adults: a meta-analysis and qualitative review. *Ann Pharmacother* 2010;44(3):489–506. DOI: 10.1345/aph.1M332
7. Goldman RD. Efficacy and safety of acetaminophen versus ibuprofen for treating children's pain or fever: a meta-analysis. *J Pediatr* 2005;146(1):142–143. DOI: 10.1016/j.jpeds.2004.10.029
8. Barr RG, Wentowski CC, Curhan G et al. Prospective study of acetaminophen use and newly diagnosed asthma among women. *Am J Respir Crit Care Med* 2004;169(7):836–841. DOI: 10.1164/rccm.200304-596OC
9. Shaheen SO, Newson RB, Henderson AJ et al. Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. *Clin Exp Allergy* 2005;35(1):18–25. DOI: 10.1111/j.1365-2222.2005.02151.x
10. Pawankar R, Canonica GW, Holgate ST et al. Allergic diseases and asthma: a major global health concern. *Curr Opin Allergy Clin Immunol* 2012;12(1):39–41. DOI: 10.1097/ACI.0b013e32834ec13b
11. Bellavite P. Homeopathy and integrative medicine: keeping an open mind. *J Med Per* 2015;13(1):1–6. DOI: 10.1007/s12682-014-0198-x
12. Prasad R. Homeopathy booming in India. *Lancet* 2007;370(9600):1679–1680. DOI: 10.1016/S0140-6736(07)61709-7
13. Iannitti T, Morales-Medina JC, Bellavite P et al. Effectiveness and safety of *arnica montana* in post-surgical setting, pain and inflammation. *Am J Ther* 2016;23(1):e184–e197. DOI: 10.1097/MJT.0000000000000036
14. Eames S, Darby P. Homeopathy and its ethical use in dentistry. *Br Dent J* 2011;210(7):299–301. DOI: 10.1038/sj.bdj.2011.237
15. Nishant S, Himadri MC, Rakesh KS et al. Review of the role of homeopathic applications in dentistry. *Int J Oral Med Res* 2015;2(4):77–80.
16. DeSchepper L. Hahnemann revisited: A textbook of classical homeopathy for the Professional. Full of life Publ.; 2001.
17. Macedo SB, Carvalho JC, Ferreira LR et al. Effect of *arnica montana* 6 ch on edema, mouth opening and pain in patients submitted to extraction of impacted third molars. *Ärztzeitschrift Für Naturheilverfahren* 2005;46:381–387.
18. Malamed SF. Handbook of Local Anaesthesia. 5th edition. St.Louis, Missouri: Mosby Inc. 200; Chapter 14: 229.
19. Robertson A, Suryanarayanan R, Banerjee A. Homeopathic *arnica montana* for post-tonsillectomy analgesia: a randomised placebo control trial. *Homeopathy* 2007;96(1):17–21. DOI: 10.1016/j.homp.2006.10.005
20. Asher I, Pearce N. Global burden of asthma among children. *Int J Tuberc Lung Dis* 2014;18(11):1269–1278. DOI: 10.5588/ijtld.14.0170
21. Riley DS, Riley, Kraplow. *Materia Medica of New and Old Homeopathic Medicines*. Springer; 2012.
22. Urquhart E. Analgesic agents and strategies in the dental pain model. *J Dent* 1994;22(6):336–341. DOI: 10.1016/0300-5712(94)90084-1
23. 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. DOI: 10.1016/j.pain.2006.08.014
24. Abraham JI, Mathew FL. Taste masking of paediatric formulation: a review on technologies, recent trends and regulatory aspects. *Int J Pharm Pharm Sci* 2014;6(1):12–19.

25. Karow JH, Abt HP, Fröhling M, et al. Efficacy of *arnica montana* D4 for healing of wounds after hallux valgus surgery compared to diclofenac. *J Altern Complement Med* 2008;14(1):17–25. DOI: 10.1089/acm.2007.0560
26. Rainsford KD, editor. *ibuprofen: discovery, development and therapeutics*. John Wiley & Sons; 2015.
27. Mennella JA, Pepino MY, Reed DR. Genetic and environmental determinants of bitter perception and sweet preferences. *Pediatrics* 2005;115(2):e216–e222. DOI: 10.1542/peds.2004-1582
28. Von Baeyer CL. Children's self-reports of pain intensity: scale selection, limitations and interpretation. *Pain Research & Management* 2006;11(3):157–162. DOI: 10.1155/2006/197616