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Original Article

Practice of L-Asparaginase Usage: A Survey among Healthcare Providers Treating Children with Cancer in India

Archana MV[1] Kalasekhar VS[2] Vinay Munikoty[1] Ramitha R. Bhat[1] Atul Achyutrao[1] Vani Lakshmi R[3] Vasudeva Bhat K[1]

[1] Division of Pediatric Hematology and Oncology, Manipal Comprehensive Cancer Care Centre, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, India.
[2] Department of Pediatric Oncology, Regional Cancer Centre, Trivandrum, Kerala, India
[3] Department of Data Science, Prasanna School of Public Health, Manipal Academy of Higher Education, Manipal, Karnataka, India

Address for correspondence Vasudeva Bhat K., MD, DM, Division of Pediatric Hematology and Oncology, Manipal Comprehensive Cancer Care Centre, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, Karnataka, 576104, India (e-mail: vasudev.bhat@manipal.edu).

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Abstract

Vasudeva Bhat K

Introduction L-asparaginase is an essential chemotherapeutic agent in the therapy of acute lymphoblastic leukemia (ALL), which has led to improvement in survival. In low- and middle-income countries like India, the outcomes in ALL are inferior compared with the published literature, one of the causes of which is believed to be due to the inferior quality of bioequivalent asparaginase.

Objective The following survey attempts to understand the practice of using this agent among oncologists treating children with cancer in our country.

Methods The researchers designed a structured online questionnaire comprising 25 aspects of L-asparaginase usage in the study. The questionnaire was directed to the healthcare providers involved in treating children with cancer in India.

Results Of the total 80 responses recorded, 51 (64%) respondents had more than 5 years of experience in pediatric oncology and were treating at least 5 to 10 newly diagnosed ALL patients per month. Forty-one (51%) respondents utilized native asparaginase, and 21 (26.3%) oncologists used PEGylated-asparaginase exclusively. The most common route of administration was the intramuscular route (66.3%). Seventy percent of respondents utilized native form at a dose of 10,000 IU/m^2 and 20% at 6,000 IU/m^2. The amounts used for PEGylated L-asparaginase were 1,000,IU/m^2, 2,500,IU/m^2, and variable doses in 48, 40, and 10% of responses, respectively. Though serum asparaginase assay (SAA) was not measured routinely in most of the centers, 39 (48.8%) healthcare providers perceived performing SAA helps to make the clinical decision.

Conclusion This survey shows a wide variation in L-asparaginase usage among healthcare providers caring for children with cancer in our country. As L-asparaginase is the pivotal component of ALL therapy, uniformity in its usage and dosing with the possibility of monitoring SAA due to the quality of bioequivalent may be one of the critical steps toward improving outcomes in ALL in our country.

Keywords
- asparaginase
- oncologists
- pediatric ALL

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer in children as it represents approximately 25% of cancer diagnoses among children below 15 years. Management of ALL has evolved over many decades; with a risk-based approach, treatment intensification, and better supportive care, survival rates in children have progressively risen to nearly 90%.[1] L-asparaginase is an integral component of treatment for children with ALL and since its introduction by the Dana Farber group in 1977 into pediatric treatment protocols survival has significantly improved.[2,3]

There are three currently available L-asparaginase preparations approved for clinical applications: *Escherichia coli*-derived native *E. coli* asparaginase, PEGylated asparaginase (PEG asparaginase), and Erwinia chrysanthemi derived Erwinia Asparaginase. All presently available asparaginase preparations share the same mechanism of action—the deamination and depletion of asparagine, an essential amino acid for the lymphoblast. Yet, each displays a markedly different pharmacokinetic profile.[4,5] PEG asparaginase has a significantly longer half-life and is less immunogenic than the native asparaginase.[6] When used in front-line therapy to replace native asparaginase as part of combination chemotherapy, PEG asparaginase has shown comparable efficacy.[7]

In clinical practice, the enzyme is currently given by the intravenous (IV), intramuscular (IM), or subcutaneous route, with dosages being different across various protocols followed.[8] Asparaginase activity of 100 IU/L at desired time point for the molecule is considered to be sufficient for complete asparagine depletion.[9] Although this might theoretically result in different pharmacokinetic profiles, information on the comparability of the routes of administration is limited about the currently available preparations.

Therapeutic drug monitoring of serum asparaginase activity (SAA) level helps individualize asparaginase dosing. The common side effects encountered with asparaginase are hypersensitivity reactions, silent inactivation, cerebral sinus venous thrombosis, pancreatitis, hyperglycemia, hypertriglyceridemia, and liver dysfunction (hyperbilirubinemia and transaminitis). There is heterogeneity among healthcare providers in the usage of L-asparaginase concerning preparations used, doses and route of administration, therapeutic drug monitoring, and toxicity profile observed along with dilemma of choosing a bioequivalent drug. The present survey attempts to understand the asparaginase usage practice among healthcare providers in India, which will pave the way for effective designing of future clinical trials associated with pediatric oncology.

Methodology

A descriptive cross-sectional survey design was employed to assess the L-asparaginase usage practice among healthcare providers treating children with cancer in India. The survey was conducted through the smart survey platform. The potential participants for the study were faculty who had registered for National continuing medical education (CME) of Pediatric Hematology and Oncology held in December 2020 virtually. The sampling bias was avoided by sending the survey link through email to all faculty who attended the CME. The researchers sent fortnightly reminders to the participants during the data collection process to minimize the nonresponses. Data collected through this platform was digitally stored in a designated device as an encrypted file. The data was transferred and securely stored in a hard drive upon completing the data collection process.

The researchers have designed a three-part survey containing 25 questions to collect data from study participants. The first part consisted of information about the survey and consent. The second part included five questions to capture the demographic details of the survey participant, and the last part had 20 questions aimed to assess the asparaginase usage practices of the respondents. It was mandatory to answer all the 25 questions prior to submitting. Out of the 20 core questions, 14 were multiple choice questions, and the remaining 6 were dichotomous questions. A pilot survey on five pediatric oncologists was implemented to check content validity and comprehensibility, of the questionnaire, the results of which were excluded from the present data analysis.

The participant's responses to the survey questionnaire were recorded on Microsoft Excel 2016 and quantitatively analyzed using IBM SPSS 16.0. Descriptive statistics were implemented in the present study. The Institutional Ethics Committee (IEC), Kasturba Hospital and Kasturba Medical College, Manipal (IEC 532/2020) approved the study protocol.

Results

Out of the 215 participants who had registered for the CME, 120 faculty (junior and senior consultants) excluding trainees were sent the link for the survey. Of these 120 faculty, response was received from 80 healthcare providers treating children with cancer across India. The failure rate was 33%. The demographics of the healthcare providers participating in the survey is presented in ►Table 1.

Type and Dose of Asparaginase

The most common asparaginase used by Indian pediatric oncologists is native *E. coli* asparaginase. Forty-one (51.2%) respondents used the native form exclusively, whereas 21 (26.3%) respondents used PEGylated asparaginase exclusively and 18 (22.5%) respondents used both forms (►Fig. 1). Erwinia asparaginase is unavailable in India and was not used. There was no statistically significant relationship between the practice setting and the type of asparaginase used by the healthcare providers ($p = 0.489$). There was significantly more utilization of PEG asparaginase among participants who had 5 to 10 years of experience ($p = 0.04$). Fifty-six (70%) respondents used 10,000U/m^2/dose of native asparaginase. Sixteen (20%) and 8 (10%) respondents used native asparaginase at 6,000U/m^2/dose and variable dose, respectively. Most of the participants (78%, $n = 62$) used a 72-hour dosing interval while administering native asparaginase. In

Table 1 Demographics of healthcare providers participating in the survey

Characteristics	Frequency (percentage)
Your area of specialization	
Pediatric hematology	1 (1.2)
Pediatric hematology and oncology	60 (75)
Pediatric oncology	19 (23.8)
Gender of the participant	
Male	42 (52.5)
Female	38 (47.5)
Work experience in your specialization (in years)	
<5	29 (36.2)
5–10	32 (40)
>10	19 (23.8)
Practice setting	
Exclusive private practice	11 (13.8)
Government/aided institute	13 (16.2)
Private practice affiliated with the institute	16 (20)
University/academic institute	38 (47.5)
Others	2 (2.5)

the case of PEGylated asparaginase, 39 (48.8%), 32 (40%), and 9 (11.3%) respondents utilized 1000U/m^2/dose, 2500U/m^2/dose, and variable dose regimen, respectively. When asked about the preferred route of administration of asparaginase, 66% ($n=53$) used the IM route and 29% ($n=23$) respondents gave the drug by IV route, details of which are depicted in ►**Fig. 2**.

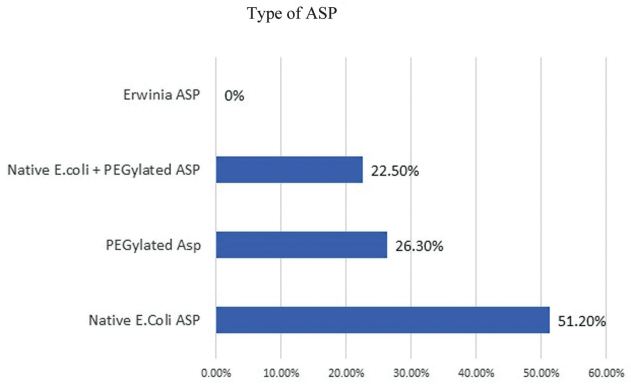

Fig. 1 Frequency of utilization of different types of asparaginase (ASP). *E. coli*, *Escherichia coli*.

Side Effect Profile

To understand the side effect profile of asparaginase, participants were asked multiple-choice questions with options consisting of various side effects of asparaginase such as hypersensitivity reaction, liver dysfunction (hyperbilirubinemia and transaminitis), hyperglycemia needing medication, cerebral sinus venous thrombosis, and pancreatitis. Further to this question elaborated the phase in which side effects were observed (induction vs. reinduction/delayed intensification), and the type of asparaginase utilized. The most common side effect observed by survey participants is hypersensitivity reaction followed by liver dysfunction. Frequency of hypersensitivity reaction was more in reinduction (40% in induction vs. 72% in reinduction with respect to native asparaginase). As per the respondents, the frequency of hypersensitive reactions was lesser with the utility of PEG asparaginase as compared with native formulation, which was statistically significant ($p=0.01$). The side effect profile, route of administration, and the dose of asparaginase (native or PEGylated) lacked correlation with adverse events. The side effect profile is presented in ►**Fig. 3**.

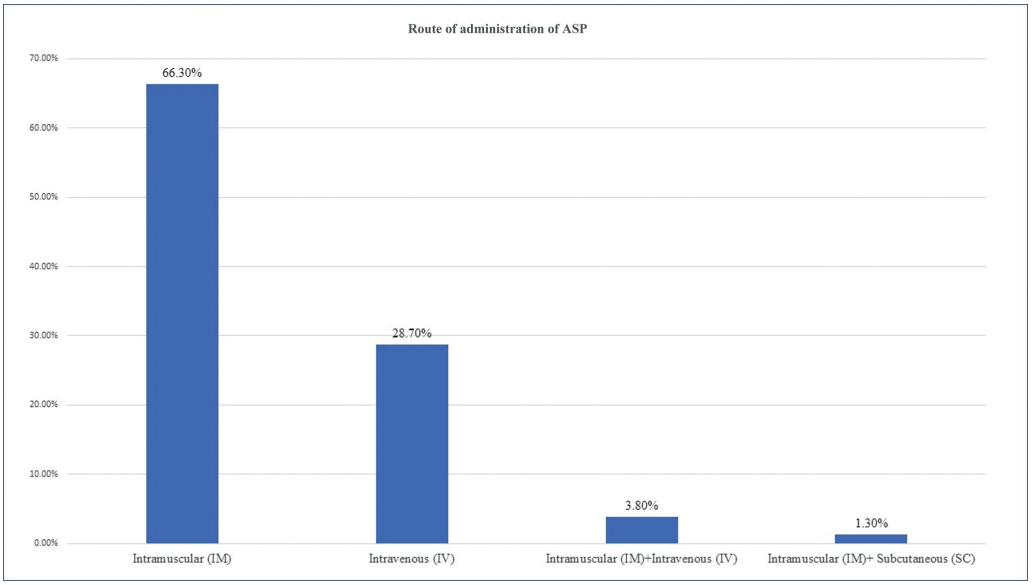

Fig. 2 Preferred route of administration of asparaginase.

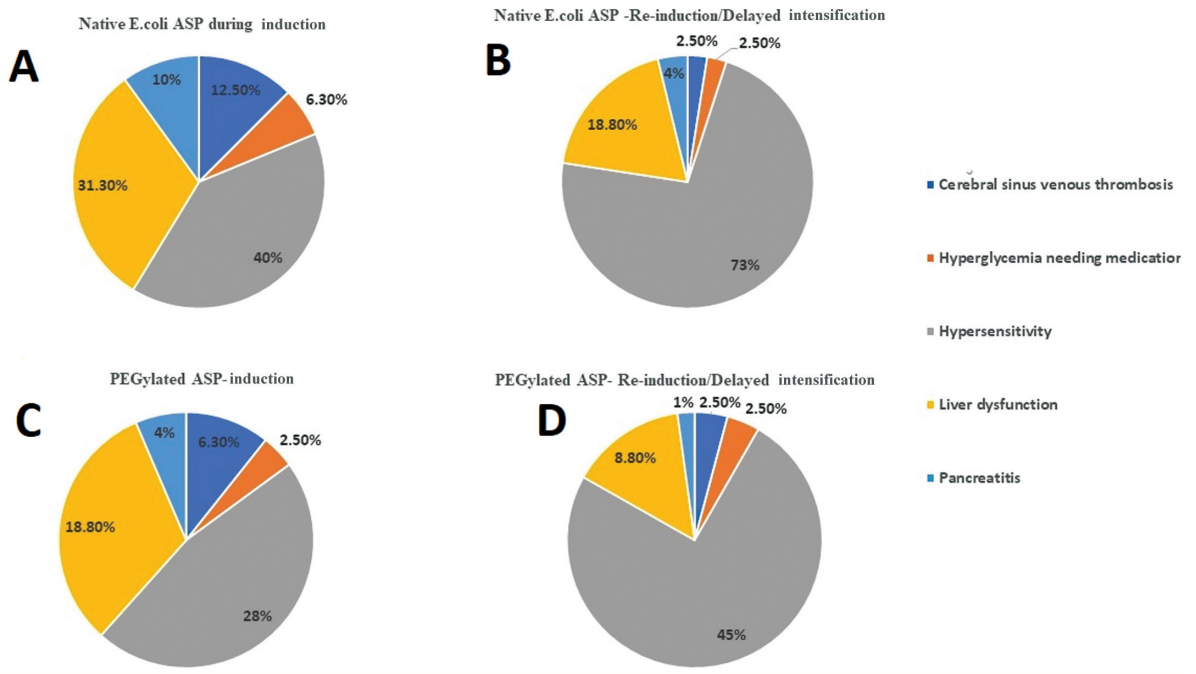

Fig. 3 Side effects profile of asparaginase (ASP) as observed by pediatric hematologists and oncologists in India. (**A**) Side effect frequency of native *Escherichia coli* ASP during induction. (**B**) Side effect frequency of native *E. coli* ASP during reinduction/delayed intensification. (**C**) Side effect frequency of PEGylated ASP during induction. (**D**) Side effect frequency of PEGylated ASP reinduction/delayed intensification.

Facts and Perception about Asparaginase Usage

Though the most common side effect observed was hypersensitivity reaction, 58% ($n = 47$) of responders were willing to rechallenge L-asparaginase. In 67% of instances, participants opted to re challenge with PEG asparaginase, and 16% with native *E. coli* asparaginase. Forty-four responders (55%) rechallenged the drug under premedication. When participants were asked whether they are willing to rechallenge patients who developed pancreatitis to native L-asparaginase in the past, during reinduction/delayed intensification, 61 responders (76.3%) were against rechallenging versus 19 who are willing to rechallenge.

Though more than 50% of participants are utilizing the drug within 24 hours of opening the vial, nearly 45% of responders are storing the leftover drug for future use. Most ($n = 75$, 94%) clinicians neither measured serum fibrinogen level routinely nor did they give fresh frozen plasma transfusion for replacing plasma factor.

Participants were given a dichotomous question stating do you monitor SAA level in your practice, approximately 73 responders (91%) did not do it routinely, whereas approximately 9% of participants were doing it in their practice. Further to this when participants were asked whether monitoring SAA level help in their clinical decision, 46% perceived it will benefit, whereas 48% were not sure about the clinical benefit of the same.

Discussion

This survey investigated asparaginase usage practice among healthcare providers treating children with cancer in India. Despite asparaginase being the prime catalyst in improving the outcome of pediatric ALL, there is a wide variation in its usage practice in India. PEGylated asparaginase has replaced native asparaginase for the treatment of pediatric ALL because of its prolonged effect, lower incidence of silent antibodies, similar safety profile, and convenience.[6] Many international pediatric ALL trials have shown promising outcomes with PEGylated asparaginase.[10,11] Despite this in India, most survey participants use native formulation probably due to the higher cost and nonavailability of PEGylated formulation under certain national health schemes. As per this study, respondents majorly utilized the IM route, perhaps because this method is less time-consuming, does not require a test dose to be given, and has ease of administration especially in high-volume centers. There was no statistically significant difference in reporting of mean hypersensitivity reaction rate between the IM and IV route, which is in accordance with the randomized study by the Dana Farber group.[12]

Incidence of hypersensitivity reaction varies depending on formulation, route, and frequency of administration. These hypersensitivity reactions are mediated by neutralizing antibodies in most instances. However, with the use of IV PEGylated asparaginase, a distinct type of acute clinical reaction (a non-allergic infusion reaction) is becoming increasingly recognized, and it is nearly impossible to distinguish this reaction from allergic hypersensitivity clinically. In this survey, hypersensitivity reaction was the most common adverse event noticed by participants, even for PEGylated asparaginase during induction chemotherapy. As per a well-known study, a policy of universal premedication to prevent

infusion-related reaction with therapeutic drug monitoring might significantly benefit our patient.[13]

As per the study findings, more than 90% of participants did not carry out therapeutic drug monitoring, but nearly 50% of participants felt that it would benefit their clinical decision. A study highlights the importance of therapeutic drug monitoring in individualized PEGylated asparaginase dose.[14] However, in the present study, participants opted to premedicate while rechallenging asparaginase without monitoring drug level, which might mask allergic reaction resulting in subtherapeutic levels hampering desired outcomes. As per the experiences from two oncology center in India, there was a concern regarding unsatisfactory quality and therapeutic activity of biogeneric native asparaginase marketed in India.[15,16] A prospective observational study from North India demonstrated that achievement of adequate SAA level with generic brands of PEGylated asparaginase. This could be the way forward for low-to-middle income country to utilize economical generic brands along with therapeutic drug monitoring.[17]

The side effect profile seen in India is almost similar to the side effect seen worldwide.[18] Apart from an allergic reaction, another common reason for discontinuing asparaginase therapy is pancreatitis; nearly 75% of survey participants were not re-exposing the drug following an episode of asparaginase-associated pancreatitis. There is a significant negative impact of discontinuing asparaginase, especially in high-risk patients.[19] Hence, the decision to discontinue should be taken with caution, considering the severity of the initial episode and additional risk factors for pancreatitis.[20] There is a need for prospective studies to define "rechallenge strategy" following asparaginase-associated pancreatitis.

The present survey utilized an online method to obtain information from participants across the country. There were instances of multiple participants from the same institute/hospital vis-a-vis no representation from a few institutions. Although the data from the survey can be utilized for identifying research gaps and proposing research questions, the survey results cannot be extrapolated for clinical use.

In conclusion, this survey shows a wide variation in L-asparaginase usage among healthcare providers caring for children with cancer in our country concerning the formulation, dose and route of administration. As L-asparaginase is the pivotal component of ALL therapy, uniformity in its usage and dosing is the need of the hour. With the availability of multiple generic brands, therapeutic drug monitoring of SAA should be a critical step toward improving outcomes in ALL in our country. We need prospective nationwide studies to define optimal asparagine depletion and the level of enzyme activity required in our population.

Note

Presented as a poster in 53rd Congress of the International Society of Pediatric oncology (SIOP), virtual congress, October 21 to 24, 2021

Authors' Contributions

Archana MV designed the study design, collected data, and written manuscript. Vasudeva Bhat conceptualized the research, prepared the study design, and approved the final version of the manuscript. Kalashekar VS and Vinay Munikoty reviewed and approved the final version of the manuscript. Vanilakshmi analyzed the data. Ramitha and Atul helped with data collection and edited manuscript. All authors have contributed to the manuscript in significant ways and have reviewed and agreed upon the manuscript content.

Review Board Approval

The Institutional Ethics Committee (IEC), Kasturba Hospital and Kasturba Medical College, Manipal (IEC 532/2020) approved the study protocol.

Conflicts of Interest

None.

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