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ACCIDENTAL INTRATHECAL TRANEXAMIC ACID ADMINISTRATIONS DURING SPINAL ANAESTHESIA AND THEIR REPORTING IN INDIA - A NARRATIVE REVIEW

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ABSTRACT: Look-alike ampoules of tranexamic acid and local anaesthetic heavy bupivacaine are available, leading to accidental administration. We aimed to investigate India-specific incidents of intrathecal tranexamic acid (TXA) administration during spinal anaesthesia to identify manufacturing issues. Our secondary aim was to determine the availability of any national drug error reporting and monitoring system for hospitals in India. The author investigated published ten reports (11 patients) from India of TXA administration intrathecally in place of heavy bupivacaine. In all mistakes of look-like TXA and local anaesthetic (LA) (heavy 0.5% bupivacaine), ampoules were present in operating rooms. We found three manufacturers who designed, manufactured, and supplied identical TXA and heavy bupivacaine ampules. In addition, there was also a similarity of TXA and LA ampoules among different manufacturers. We searched PubMed and Google Scholar for any publication on India's national medication error reporting system for hospitals. There was no publication on the national medication safety system involving hospitals. Our study shows intrathecal TXA errors occurred in east-to-west and north-to-south locations. However, there is no national medication error and reporting system to alert health care providers. We highlight potential difficulties and barriers to creating a national mechanism to notify, monitor, and prevent medication errors in hospitals in India.

INTRODUCTION: The incidence of drug errors in hospitals in India and the associated severity of harm are unknown [1]. In anaesthesia, the risk of incorrect drug administration is always present due to multiple human and systemic factors [2, 3]. In recent years, worldwide, several accidental intrathecal tranexamic acid (TXA) administrations have occurred during spinal anaesthesia, including in India (**Fig. 1**,) [4]. For a large country such as India, a national drug error reporting and monitoring system may prevent TXA-associated wrong route administration errors involving key stakeholders, including the pharmaceutical industry and healthcare providers. We aim to analyse published incidents of inadvertent TXA administration in place of 0.5 % heavy bupivacaine during spinal anaesthesia in India. The secondary objective was to investigate India's current national scenario for drug error reporting, monitoring and prevention.

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METHODS: The author investigated intrathecal administration errors in India from his two published reviews on intrathecal TXA errors during spinal anaesthesia [4, 5]. Using the previously reported strategy, the author did additional PubMed and Google Scholar searches to find any recent reports of intrathecal TXA administration errors in India till August 2023. TXA and heavy bupivacaine manufacturers were identified from the articles, either from the text or image provided. The corresponding author was contacted to obtain details when the manufacturer's information was not provided in the report. From the reports included, learned lessons were recorded as highlighted in the original published reports. The author recorded the Indian city where the error

occurred. To determine the availability of national drug error reporting and monitoring in India, the author searched PubMed adopting the search strategy: (Medication error [TIAB] OR Drug errors [TIAB] OR Adverse drug reaction [TIAB]) AND (Reporting [TIAB] OR Monitoring [TIAB] OR Prevention [TIAB] OR Audit [TIAB] OR System [TIAB] OR Portal [TIAB]) AND (India [TIAB] OR Indian [TIAB] OR State [TIAB] OR Union territory [TIAB]). A second PubMed search was performed using the phrases 'drug error reporting India', 'medication error reporting in India', 'drug error monitoring India' and 'medication error monitoring in India'. In addition, the author searched Google Scholar using the phrases 'drug error reporting India', 'medication error reporting in India', 'drug error monitoring India' and medication error monitoring in India'. For Google Scholar, the 'all in title' restriction was applied.

RESULTS: Of 37 published errors (43 patients) in two publications [4, 5], ten publications (11 patients) reported accidental intrathecal TXA administration during spinal anaesthesia for various surgical patients (caesarean delivery -4, orthopaedic -3, urology-2, general surgery-2) [6-15]. The errors occurred in hospitals from several regions of India **Table 1.**

TABLE 1: PUBLISHED REPORTS OF ACCIDENTAL INTRATHECAL ADMINISTRATION OF TRANEXAMIC ACID DURING SPINAL ANAESTHESIA IN INDIA

Reference, Author, Journal, Year	City (State)	Tradename (company) Tranexamic acid Bupivacaine	Learning points identified /Changes implemented/comments	Outcome
6. Garcha *et al.* Anesth & Analg 2007	Pune (Maharashtra)	Tranfib (Cipla Limited) Anawin (Neon laboratories)	Not mentioned.	Death
7. Butala *et al.* Ind J Anaesth 2012	Ahmedabad (Gujarat)	Nexamin (Medimark Biotech) Sensovac Heavy (Medimark Biotech)	Double checking is important. Some manufacturers have changed the configuration of bupivacaine ampoule.	Survived
8. Shrivastava *et al.* Internet J Anesthesiol 2012	Agra (Uttar Pradesh)	Trenaxa (Macleod's Pharmaceuticals) Senosrcaine heavy (?Company)	Identification of drug mandatory for anaesthetists. Operating room specific medication safety programme.	Death
9. Ragu K *et al.* Int J Neuro & Spine Sci 2013	Nellore (Andhra Pradesh)	Not mentioned / no image	Drug manufacturers should take measures to differ colour coding.	Death
10. Goyal *et al.* J of Acute Care Med 2014	Udaipur (Rajasthan)	Not mentioned / no image	Unique manufacturing of critical drugs such as local anaesthetics is important.	Survived
11. Roy *et al.* Southeast Asian J of Case report & review 2015	Calcutta (West Bengal)	Cylokrypton (Astra Zeneca) Sensorcaine Heavy (Astra Zeneca)	Standardised arrangement of medications, reading the label, manufacturing different size, shape, color and labelling of ampoules.	Survived
12. Narra* J of Res in Anesthesiol & Pain Med 2015	Nalgonda (Telangana)	Klotin (Neon laboratories)/T Stat (Mercury Pharmaceuticals) Anawin (Neon laboratories)	Manufacturers should be directed to change design of bupivacaine ampoules.	Survived
13. Shah *et al.* Ind J Anaesth (two patients) 2021	Raipur (Chhattisgarh)	Could not be read from the image in the article	Wrote to government and manufacturer to change in look-alike ampoules. Double checking. Medication errors awareness programme.	Patient 1: Survived Patient 2: Death: (undelivered baby also died)
14. Kumari R. J Anes and Patient Care 2022	New Delhi (New Delhi)	Not mentioned / no image	Two different ampoules had a similar appearance. Double checking is important.	Survived
15. Singh *et al.* J of South Asian Fed Obst Gynae 2022	Mau (Uttar Pradesh)	Not mentioned / no image	Properly standardized drugs in the operating room, sensitization of working staff, proper training, label should be read.	Survived

Six reports (seven patients) included images of the ampoule and the names of the manufacturer (pharmaceutical company). When included, images were of glass ampoules. In three incidents, the hospital had procured look-alike TXA and heavy bupivacaine ampoules from the same company **Table 1**. In other words, three manufacturers designed, produced and supplied look-alike TXA and heavy bupivacaine ampoules. In addition, two error publications showed identical ampoules by two different manufacturers. Several authors expressed concerns about the design/manufacturing of TXA and heavy bupivacaine ampoules **Table 1.** One author wrote to the government and manufacturers to act on the look-alike ampoules [13]. A PubMed search for drug error reporting or monitoring systems in India retrieved 572 results (combining two separate investigations), and Google Scholar retrieved three results. None of the retrieved articles were specific publications on national drug error reporting or monitoring systems in hospitals in India.

DISCUSSION: TXA has been available for clinical use as an antifibrinolytic agent for the last five decades. In recent years, the clinical indications of TXA have increased, as evidenced by its beneficial effect in reducing blood loss and the requirement of allogenic blood transfusion for various critical medical and surgical conditions [16]. **Fig. 2** highlights intrathecal tranexamic acid administration errors in the last decade due to look-alike heavy bupivacaine ampoules (in India and other countries) or vials (in North American countries). **Table 2** shows a database for known intrathecal TXA errors during spinal anaesthesia.

TABLE 2: DATABASE OF INTRATHECAL TRANEXAMIC ACID ADMINISTRATION ERRORS DURING SPINAL ANAESTHESIA

Reference 4:21 reports, Reference 5:22 reports, Reference 12: Three deaths mentioned in the publication.	
Additional reports (Published in journals, Safety agency alerts, Blog, Media):	
1	Lew GS, Ryoo ST, Soung HC, Joo JC. A case report of central nervous system toxicity following accidental Injection of tranexamic acid into subarachnoid space. Korean J Anesthesiol 1993; 26:1300-5.
2	Yi Chun Jung, Sang Ho Lee *et al.* Two case reports of seizure following inadvertent injection of tranexamic acid into subarachnoid space. Korean J Anesthesiol 1994; 27:1686-91.
3	Blog: Rex Russell. Case reports in Anaestheisa. June 2014. http://russellmd.blogspot.com/search/label/tranexamic%20acid
4	Alam MR. Spinal needle with prefilled syringe to prevent medication error: A proposal. Ind J Anaesth 2016; 60:525.
5	Institute for safe medication practices Safety alerts: (1) May 2019. https://www.ismp.org/resources/dangerous-wrong-route-errors-tranexamic-acid-major-cause-concern (one case reported) (2) Sep 2020. https://www.ismp.org/alerts/dangerous-wrong-route-errors-tranexamic-acid(three patients reported) (3) ISMP Canada. Alert: substitution error tranexamic acid during spinal anaesthesia. ISMP Can Saf Bull 2022; 6:1–5. (One more case mentioned).
6	Moran NF, Bishop DG, Fawcus S etal. Tranexamic acid at cesarean delivery: drug-error deaths. BJOG 2023; 130:114-117(Three cases mentioned. 2 deaths and one residual neurologic deficit).
7	Media report (April 2022) : https://www.star-telegram.com/news/local/article260155335.html
8	Costa L, Costa M, Martins Jet al.Polymyoclonus, ventricular fibrillation and Takotsubo after accidental spinal injection of tranexamic acid. BMJ Case Reports CP 2023; 16:e251814. http://dx.doi.org/10.1136/bcr-2022-251814

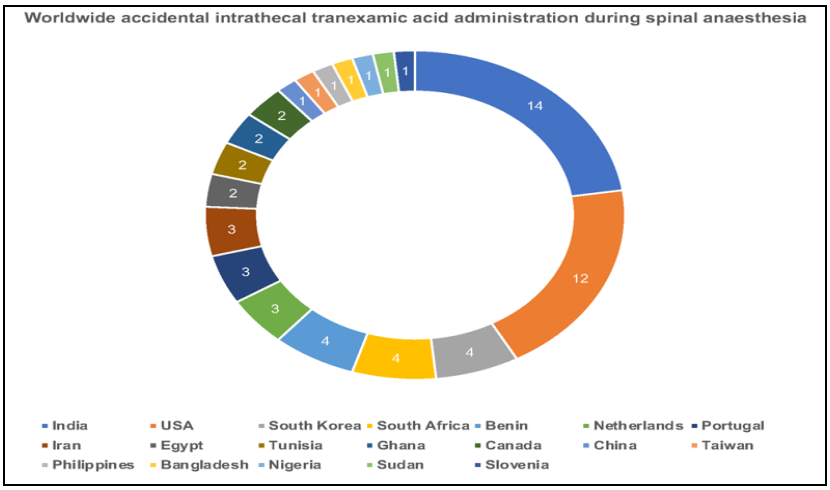

FIG. 1: WORLDWIDE INTRATHECAL TRANEXAMIC ACID INCIDENTS DURING SPINAL ANAESTHESIA. FOR INDIA INCIDENTS, FOR THREE PATIENTS, NO DETAILS EXCEPT DEATH OCCURRED [12]

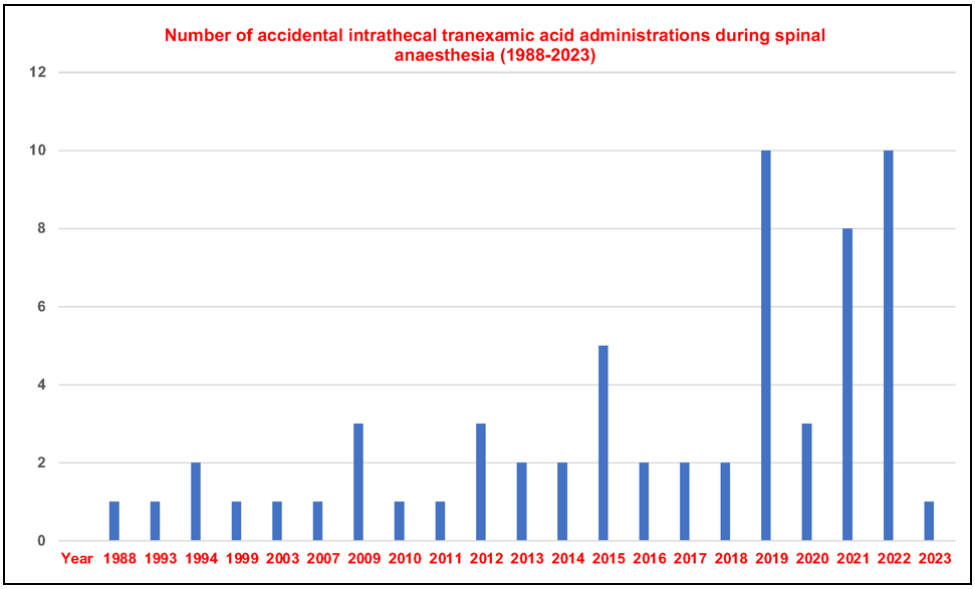

FIG. 2: INTRATHECAL TRANEXAMIC ACID ADMINISTRATION ERRORS DURING SPINAL ANAESTHESIA FROM 1988 TO 2023

Of the known mistakes of intrathecal TXA, 25% of incidents have occurred in India **Fig. 1**. Characteristically, intrathecal TXA is associated with mortality or severe morbidity in 50% and life-threatening systemic complications in surviving patients [5-15].

The previous review described pathophysiological complications and clinical management, including cerebrospinal fluid aspiration/drainage and critical care [4, 5]. There are multiple (>50 as per the author's preliminary search on the internet) manufacturers/suppliers of TXA in India [17]. Theoretically, it may increase the problem of manufacturing/designing issues of TXA ampoules and increase the risk of identical design/manufacturing with other widely used medications such as local anaesthetics. There is little evidence on the role of manufacturers and regulatory bodies in preventing medication errors [18]. Some factors that may prevent manufacturers from getting involved include legal implications, regulatory interference, and loss of competitive advantages [18].

In India, these mishaps occurred in hospitals in the east, west, north, or south regions **Table 1**. In addition, Reddy reported three more deaths in the same city [12]. Another crucial practical point is that anaesthetic and other medications are often prescribed on the day of surgery, which are then bought over the counter. It gives very little time to anaesthetists or their assistants to organize anaesthesia workstations, particularly for anaesthetists who do freelance private practice in smaller hospitals. As the risk is persistent, preventive measures are necessary, including separate storage for TXA and heavy bupivacaine ampoules, additional labelling of ampoules, double checking (e.g. with other health care providers or, if available with bar code reader), awareness and education of staff, communication if any change in supply, alternative form of preparation (e.g. pharmacy prepared TXA infusion bag). These incidents prompt debate on the existence of robust drug error-detecting mechanisms in government and private hospitals. A survey of 9000 anaesthesiologists (response rate 9.2%) registered with the Indian Society of Anaesthesia found that most respondents have experienced drug administration errors at some point in their careers [19]. The authors suggested that a dedicated system, including one at the national level, is necessary to report medication errors, identify causes, and minimise them.

In 2012, a study found that no national drug error reporting and monitoring system was available for hospitals in states or union territories of India [20]. Until good quality data are collected and analysed, it would be impossible to assess baseline prevalence rate and contributory events for perioperative medication errors such as intrathecal TXA [22]. However, the development of a national medication error reporting system in India may be

complex and require overcoming difficulties due to regional (e.g. language barrier) and state (e.g. inclusion of all urban, district and rural hospitals) and national (e.g. governance) hurdles. Nevertheless, such a mechanism has potential benefits, including identifying regional variations of drug errors, monitoring the burden of errors (e.g., patient harm, financial implications), improving the knowledge about contributory factors, alerting relevant stakeholders and implementing measures to correct identified latent and active deficiencies [22]. Furthermore, a successful system would require adequate resources, technological innovation, effective collaboration among state and central government agencies, hospital cooperation, and responsible healthcare providers keeping the principle of beneficence report error reports with all relevant details to learn lessons [22].

WHO established a pharmacovigilance programme as one mechanism for reporting adverse drug reactions. Suke *et al.* have described the current structure and functioning of the pharmacovigilance program in India (PVPI), whose objective is to collect data on adverse drug reactions *via* adverse drug reaction (ADR) monitoring centres in government, private or charity hospitals [23]. However, pharmacovigilance has several flaws, including lack of reporting or underreporting from health workers, poor quality of data and lack of audits [24]. For hospital settings, challenges for PVPI include improving awareness among clinical and pharmacy staff, infrastructure deficiencies (e.g. trained staff, communication tools), lack of collaboration among centres and dissemination of the lessons learned from adverse medication-related incidents. However, in India and other developing countries, the challenge to minimise medication errors in high-risk incidents such as intrathecal TXA in operation theatres still needs to be addressed and requires multidisciplinary brainstorming involving relevant stakeholders.

Limitations: Severe events such as those analysed in this investigation are underreported. In India, errors in smaller district hospitals or during free-lance practice may not be recognised and reported because of fear and loss of work/practice. Therefore, it is difficult to determine the actual number of intrathecal TXA incidents in India. Some reports neither mentioned the manufacturer nor provided images of the ampoules. Most reports should have elaborated on the working environment, local high-risk medication handling procedures and training, or the number of personnel involved.

CONCLUSION: Inadvertent intrathecal administration of TXA during spinal anaesthesia is a risk in various regions of India. Currently, prevention should be focused locally by identifying local deficiencies and adopting measures to improve them. There is a need to standardise TXA ampoule design/product in India and other countries. The national medication error reporting and monitoring may facilitate reporting and preventing devastating TXA and other high-risk medication errors in hospitals.

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