Advisory for healthcare service providers

Diagnosing and treating Thrombosis and Thrombocytopenic Syndrome (TTS) occurring after administration of COVID-19 vaccine

Reports of rare cases of thrombosis associated with thrombocytopenia have been reported globally from some countries following the use of some COVID 19 vaccinations particularly AstraZeneca vaccine [Covishield in India] and Johnson & Johnson's Janssen vaccine. These cases have been reported to have occurred within two to three weeks of vaccination, mostly after the first dose; younger than 60 years and women were observed to have a higher risk of the problem. Drug regulators of EU, UK and USA are investigating these reports. A causal relationship between these rare events has not been established at this time[1]. WHO has stated[2] that a causal relationship between the ChAdOx-1S vaccine (AstraZeneca/Covishield) and Thrombosis with Thrombocytopenia Syndrome (TTS) (a very rare syndrome of blood clotting combined with low platelet count reported about 4 to 20 days following vaccination) is considered plausible although the biological mechanism for the syndrome is still being investigated.

In India, the National AEFI Committee has reviewed 498 serious and severe adverse events following COVID-19 vaccinations to identify TTS - thromboembolic events (such as Cerebral Venous Sinus Thrombosis, Deep Vein Thrombosis and Pulmonary Embolism) in association with thrombocytopenia. Only a few cases clinically compatible with the diagnosis of TTS has been identified among these 498 cases which constitute a miniscule part of the total doses administered, such cases were reviewed. If these cases are considered as suspected TTS, the reporting rate of these events in India would be around 0.61/million doses, which is much lower than the 4 cases / million reported by UK's regulator (MHRA) or the 10 cases / million doses reported by Germany. Based on UK's reporting rate, there should have been 360 cases of TTS in India with 9 crore doses administered. Published scientific literature shows that thromboembolic phenomenon is almost 70% less in South East Asian population compared to those of European descent[3,4,5] .

Available AEFI data from India does not suggest any overall increase in clotting conditions such as deep venous thrombosis or pulmonary embolism following administration of COVID-19 vaccines. Reported rates of thromboembolic events after COVID-19 vaccines are in line with the expected number of

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[1] EMA Statement: https://www.ema.europa.eu/en/news/covid-19-vaccine-astrazeneca-benefits-still-outweigh-risks-despite-possible-link-rare-blood-clots
UK MHRA statement: https://www.gov.uk/government/news/uk-regulator-confirms-that-people-should-continue-to-receive-the-covid-19-vaccine-astrazeneca

[2] WHO-GACVS statement of 21 April: https://www.who.int/publications/i/item/WHO-2019-nCoV-vaccines-SAGE_recommendation-AZD1222-2021.1

[3] Lee LH, Gallus A, Jindal R, Wang C, Wu CC. Incidence of Venous Thromboembolism in Asian Populations: A Systematic Review. Thromb Haemost. 2017 Dec;117(12):2243-2260. doi: 10.1160/TH17-02-0134. Epub 2017 Dec 6. PMID: 29212112. https://pubmed.ncbi.nlm.nih.gov/29212112/

[4] White RH, Keenan CR. Effects of race and ethnicity on the incidence of venous thromboembolism. Thromb Res. 2009;123 Suppl 4:S11-7. doi: 10.1016/S0049-3848(09)70136-7. PMID: 19303496. https://pubmed.ncbi.nlm.nih.gov/19303496/

[5] ZAKAI, N.A. and McCLURE, L.A. (2011), Racial differences in venous thromboembolism. Journal of Thrombosis and Haemostasis, 9: 1877-1882. https://onlinelibrary.wiley.com/doi/full/10.1111/j.1538-7836.2011.04443.x

diagnoses of these conditions. Both conditions occur naturally and are not uncommon. They also occur in patients with COVID-19 infection.

Information for healthcare professionals

Healthcare professionals should be alert to the signs and symptoms of TTS (thromboembolism and thrombocytopenia syndrome), so that they can promptly investigate and treat people affected in line with available guidelines.

Diagnosis and Management

Investigations for any suspected cases of thrombosis and thrombocytopenia:

- Blood
    - Platelet count <150x 10^9/L confirming *Thrombocytopenia*
    - Coagulation screen-raised D-Dimer values (>4000 mcg/L, suspect if the D-dimer level is 2000-4000 mcg/L)
    - Preserve serum sample for Antibodies to platelet factor 4 (PF4) which are detected using ELISA HIT assay.
- Radio-imaging studies
    - CT/MRI specifically for cerebro-vascular sinus thrombosis, haemorrhage, stroke
    - ECHO heart for pulmonary embolism
    - Radio-nucleotide studies and CT chest for pulmonary embolism
    - USG-doppler for thrombus in the portal, splenic, mesenteric veins
    - USG-doppler of the limbs for deep vein thrombosis (DVT)

Unlikely a case of TTS

- Thrombocytopenia without thrombosis with D-dimer normal or near normal and normal fibrinogen level
- Thrombosis with normal platelet count and D-dimer <2000 mcg/L and normal fibrinogen

Management of Thrombosis and Thrombocytopenic Syndrome (TTS) at a tertiary care hospital* such as District Hospital or Medical college, etc.

- Administer intravenous immunoglobulin (IV-Ig) urgently, 1 g/kg (divided into two days if needed) as this is the treatment most likely to influence the disease process.
- CORRECT fibrinogen levels if needed, to ensure level does not drop below 1.5 g/L, using fibrinogen concentrate or cryoprecipitate
- When fibrinogen is >1.5 g/L and platelets >30 x10^9/L consider starting anticoagulation. If anticoagulation is needed before then, critical illness dose Argatroban can be considered, initially without dose escalation and maintained at low dose.
- ANTICOAGULATE with non-heparin-based therapies such as DOACs (Direct-acting oral anti-coagulants), Argatroban, Fondaparinux or Danaparoid depending on the clinical picture. Bleeding and thrombotic risk needs to be carefully balanced and lower doses may be appropriate while platelet count is still low.
- Steroids and plasma exchange should be considered and in particular if there is a delay in giving IV-Ig.
- If no overt thrombosis, but thrombocytopenia with raised D Dimer, thrombo-prophylaxis with non-heparin-based anticoagulants should be considered – balancing bleeding and thrombotic risk. DOAC, fondaparinux or danaparoid can be used.

***Ambulance services should be made available for transportation/referral of the patient to the tertiary care hospital.**

AVOID following Interventions:

- Avoid platelet transfusions. Discuss any required interventions. If neurosurgery is required, this should not be delayed, and if the platelet count is <100 x10^9/L a platelet transfusion will be appropriate after, or with, IV-Ig
- AVOID all forms of heparin including heparin-based flushes. (It is unknown whether heparin exacerbates the condition but until further data is clear, this is best avoided).
- Avoid thrombopoietin receptor agonists and Antiplatelet agents.

At discharge

- Continue anticoagulation for at least 3 months. If thrombosis was only arterial, once the D-dimer, platelets and fibrinogen have returned to normal, the patient can be switched to an antiplatelet agent and continued for three months.
- Monitor the platelet count periodically to observe for possible relapse.

Contraindications for the administration of COVISHIELD in the context of TTS:

Past history of major venous and arterial thrombosis occurring with thrombocytopenia.

Reporting of suspected TTS cases:

- Suspected cases of TTS occurring within 20 days of vaccination should be reported to the vaccinator or the District Immunization Officer (DIO) in the Case Reporting Format for further reporting on Co-WIN app.

Covishield, the COVID-19 vaccine continues to have a definite positive benefit-risk profile, with tremendous potential to mitigate the severity of infections and reduce deaths due to COVID-19 across the world and in India. Over 15.3 crore doses of Covishield vaccine have been administered as of 08th May 2021 in India. The Ministry of Health and Family Welfare will continue to monitor the safety of all COVID-19 vaccines and promote reporting of suspected adverse events.

References:

1. https://www.ema.europa.eu/en/news/astrazenecas-covid-19-vaccine-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood
2. https://b-s-h.org.uk/media/19530/guidance-version-13-on-mngmt-of-thrombosis-with-thrombocytopenia-occurring-after-c-19-vaccine_20210407.pdf
3. https://www.gov.uk/government/publications/regulatory-approval-of-covid-19-vaccine-astrazeneca/information-for-healthcare-professionals-on-covid-19-vaccine-astrazeneca#pharmacodynamic-properties