

Title: Paramedic Clinically Appraised Topic (CAT)

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Title: Cushing’s Reflex is an accurate predictor of mortality and morbidity

Clinical Scenario

A paramedic crew are dispatched to a patient who has sustained a traumatic brain injury (TBI) and is now presenting with the Cushing’s Triad of hypertension, bradycardia, and irregular respirations.

PICO (Population-Intervention-Comparison-Outcome) Question

In patients with raised intracranial pressure (ICP) of varying pathology, is the Cushing’s Triad a more accurate indicator of precipitating mortality and morbidity in comparison to alterations in other physiological parameters?

Search Strategy

(“Cushing’s triad*” OR “Cushing’s reflex*” OR “Cushing’s sign*” OR “Cushing’s response*” OR “Cushing’s effect*” OR “Cushing’s reaction*” OR “Cushing’s phenomenon*”) AND (“intracranial pressure*” OR ICP*) limit to (English language AND humans AND year= 2017-current)

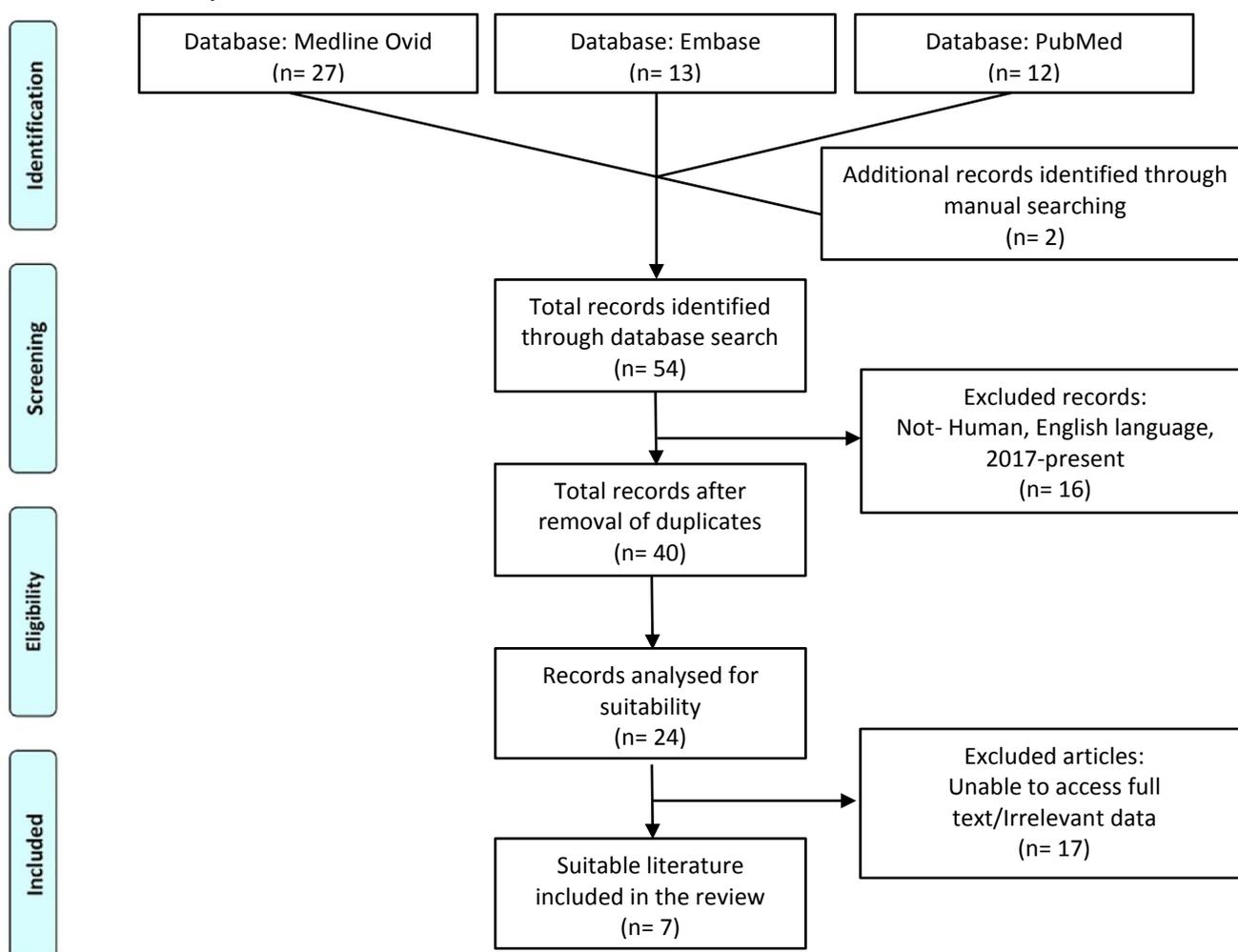


Figure 1: PRISMA flow chart displaying literature selection methods

Relevance and Rationale of the Question

Increased ICP is the most frequent cause of morbidity and mortality in patients with a TBI (Ter Avest et al., 2021). Alterations in physiological parameters, form an invaluable mechanism for detecting clinical deterioration and the requirement for immediate neurosurgical intervention. Rises in ICP are commonly associated with the Cushing's Triad, a physiological observation queried for its accuracy in predicting mortality and morbidity in brain-injured patients. The relevance of the PICO question is to therefore describe whether identification of the Cushing's Reflex provides a more accurate prediction of mortality and morbidity, in comparison to alterations in other physiological parameters including level of consciousness and pupillary response.

Table 1: Summary of relevant literature

Author, Year	Study Design (LoE)	Population: Sample Demographics	Aim	Results	Strengths and Limitations
Bhandarkar et al., 2017	Prospective, Observational Study LoE 1	10,200 patients aged >18 years with a documented systolic BP and HR between October 2013 and July 2014	To assess the relationship between HR and BP with in-hospital mortality among trauma patients	The combination of hypertension and bradycardia produced higher mortality rates (58%)	Strengths: <ul style="list-style-type: none"> - Large sample size - Identified a significant relationship between mortality and hypertension-bradycardia Limitations: <ul style="list-style-type: none"> - Lack of experimental control
Montorfano et al., 2020	Prospective, Observational Study LoE 3	16 patients aged >18 years undergoing sleeve gastrectomy	To investigate how the Cushing's reflex affects	The Cushing's reflex facilitates an oliguric	Strengths: <ul style="list-style-type: none"> - The study identified that a Cushing's

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		between 2017 and 2019	urine output and osmolality during acute elevation of ICP	response when ICP increases due to acutely elevated IAP	reflex-type response is observed in patients with abdominal compartment syndrome Limitations: - Small sample size of non-randomised patients
Schmidt et al., 2018	Prospective Study LoE 3	10 patients (mean age=65.2) with suspected normal pressure hydrocephalus	To reveal whether modest changes in ICP drive sympathetic activity	A slight rise (7mmHg) in ICP significantly increased sympathetic activity by 17% in patients	Strengths: - The study identified that ICP regulates the efferent SNS drive Limitations: - Small sample size
Ter Avest et al., 2021	Retrospective Cohort Study LoE 2	249 patients aged >18 years with a TBI between January 2016 and January 2018	To explore the diagnostic accuracy of various clinical signs (including the Cushing's Reflex) for the	In the prehospital setting, the Cushing's reflex was found to be a poor indicator of raised ICP	Strengths: - Substantial sample size Limitations: - Non-randomised selection of participants

Author, Year	Study Design (LoE)	Population: Sample Demographics	Aim	Results	Strengths and Limitations
			identification of raised ICP in the prehospital setting	following a TBI	
Tsai et al., 2018	Retrospective, Observational Study LoE 2	156 neurocritical patients screened between December 2014 and January 2018	To assess whether categorisation of the Cushing's Reflex into levels of severity produces a more accurate indication of raised ICP in comparison to non-categorisation	The severity level categorisation system proposed in the study is predictive of the outcome, and criticality of neurocritical TBI patients	Strengths: <ul style="list-style-type: none"> - Substantial sample size - Data was compressed through a linear regression model and processed by wavelet transform - Prediction accuracy of 81.6% Limitations: <ul style="list-style-type: none"> - Limited control - Lack of supporting evidence
Yumoto et al., 2017	Retrospective, Observational Study	6332 patients aged >16 years with blunt mechanism	To investigate the likelihood of life-	The combination of bradycardia	Strengths: <ul style="list-style-type: none"> - Large sample size - Extensive

Author, Year	Study Design (LoE)	Population: Sample Demographics	Aim	Results	Strengths and Limitations
	LoE 2	TBI between 2010 and 2014	threatening brain injury among trauma patients presenting with the Cushing's sign in the prehospital setting	and hypertension without an eye-opening response was a weak but significant indicator of life-threatening brain injury	data analysis <ul style="list-style-type: none"> - Established a clear relationship between the Cushing's reflex and the need for immediate neurosurgical intervention Limitations:

					Other physiological findings and variables were not taken into consideration (i.e., CT findings)
Yumoto et al., 2018	Retrospective Cohort Study LoE 2	1480 paediatric patients aged 2-15 years with a GCS motor score <5 following blunt TBI between 2004 and 2015	To analyse whether the Cushing's sign accurately predicts the requirement for immediate neurosurgical intervention amongst	Recognition of the Cushing's sign accurately predicted clinical deterioration in patients aged 7-10 and 11-15 years old	Strengths: <ul style="list-style-type: none"> - Large sample size - The study utilised a multiple logistic regression model to analyse the data Limitations:

Author, Year	Study Design (LoE)	Population: Sample Demographics	Aim	Results	Strengths and Limitations
			paediatric patients with blunt mechanism TBI		<ul style="list-style-type: none"> - Detailed patterns of injury were unavailable due to the retrospective nature of the study - Prior prehospital treatment of patients was not accounted for

Abbreviations: LoE; Level of Evidence, BP; Blood Pressure, HR; Heart Rate, ICP; Intra-Cranial Pressure, TBI; Traumatic Brain Injury, GCS; Glasgow Coma Score, CT; Computed Tomography, SNS; Sympathetic Nervous System, IAP; Intra-Abdominal Pressure

Comments

Overall, the availability of high-level literature pertaining to the PICO question was both limited and outdated. This impacted the ability to draw comprehensive and definitive conclusions regarding the accuracy of the Cushing's reflex in predicting mortality and morbidity. Although pertinent literature was of generically low quality and reliability, seven articles were found appropriate for data analysis and critique in this clinical appraisal. Across the literature, a clear association was defined between the immediate requirement for neurosurgical intervention with precipitating mortality, and the onset/identification of the Cushing's reflex in patients with a TBI. The literature demonstrated a clear association between the end-stages of raised intracranial pressure (ICP), with the presence of the

Cushing's triad. Although this relationship was observed, there is significant discrepancy existing across the literature, surrounding the overall accuracy of the Cushing's reflex in predicting mortality and morbidity following a TBI. The literature broadly attributed the Cushing's reflex with weak yet significant prognostication of life-threatening deterioration following a TBI, that may or may not be observed with concomitant alterations in other physiological variables including Glasgow Coma Score (GCS), pupillary response and urine output. It was also noted in some studies that an atypical presentation of the Cushing's reflex may be likely in patients with hypovolaemia and/or in those presenting with other comorbidities (Bhandarkar et al., 2017). Atypical presentation of the Cushing's reflex was described in the literature as the presence of tachycardia and hypertension, without an alteration in respiratory rate and function. A retrospective, observational study by Yumoto et al. (2017), described the Cushing's reflex with the addition of a no eye-opening GCS response, as a weak yet significant indicator of physiological declination precipitating death due to a life-threatening brain injury. It is clear that the Cushing's reflex is a significant and highly variable determinant of morbidity and mortality in the brain-injured patient and may or may not be associated with the presence of other significant alterations in physiological parameters.

Consider

The relevant articles suggest that recognition of the Cushing's reflex in brain-injured patients, is a weak but significant indicator of the requirement for immediate neurosurgical intervention, predictive of overall mortality and morbidity. To increase the accuracy of such diagnostic tools, it may be advantageous to investigate the degree of hypertension, bradycardia, and irregular respirations in relation to the severity of brain injury and the likelihood of morbid/mortal outcomes. It is also suggested that further research be conducted into the significance of other physiological changes observed parallel, or isolated to the Cushing's reflex, that may also be indicative of impending brain herniation and death. Reliable evidence surrounding this topic will increase the diagnostic efficacy of life-threatening brain injuries, thus leading to the hastening of appropriate medical interventions.

Clinical Bottom Line

The Cushing's reflex is a highly variable, yet significant tool utilised for the rapid identification of life-threatening brain injuries. Although historically the Cushing's reflex is defined by a triad of bradycardia, hypertension and irregular respirations, atypical presentations of the Cushing's reflex are likely and should not be overlooked by clinicians.

References

- Bhandarkar, P., Munivenkatappa, A., Roy, N., Kumar, V., Samudrala, V. D., Kamble, J., & Agrawal, A. (2017). On-admission blood pressure and pulse rate in trauma patients and their correlation with mortality: Cushing's phenomenon revisited. *International Journal of Critical Illness and Injury Science*, 7(1), 14.
- Montorfano, L., Giambartolomei, G., Funes, D. R., Lo Menzo, E., Dip, F., White, K. P., & Rosenthal, R. J. (2020). The Cushing reflex and the vasopressin-mediated hemodynamic response to increased intracranial pressure during acute elevations in intraabdominal pressure. *Surgery*, 167(2), 478-483.
<https://doi.org/https://dx.doi.org/10.1016/j.surg.2019.10.006>
- Schmidt, E. A., Despas, F., Traon, A. P. L., Czornyka, Z., Pickard, J. D., Rahmouni, K., Pathak, A., & Senard, J. M. (2018). Intracranial pressure is a determinant of sympathetic activity. *Frontiers in Physiology*, 9(11), 1-13.
<https://doi.org/10.3389/fphys.2018.00011>
- Ter Avest, E., Taylor, S., Wilson, M., & Lyon, R. L. (2021). Prehospital clinical signs are a poor predictor of raised intracranial pressure following traumatic brain injury. *Emergency Medicine Journal*, 38(1), 21-26.
<https://doi.org/https://dx.doi.org/10.1136/emermed-2020-209635>
- Tsai, Y. H., Lin, J. Y., Huang, Y. Y., & Wong, J. M. (2018). Cushing response-based warning system for intensive care of brain-injured patients. *Clinical Neurophysiology*, 129(12), 2602-2612. <https://doi.org/https://dx.doi.org/10.1016/j.clinph.2018.09.010>
- Yumoto, T., Mitsunashi, T., Yamakawa, Y., Iida, A., Nosaka, N., Tsukahara, K., Naito, H., & Nakao, A. (2017). Impact of Cushing's sign in the prehospital setting on predicting the need for immediate neurosurgical intervention in trauma patients: a nationwide retrospective observational study. *Scand J Trauma Resusc Emerg Med*, 24(1), 147.
<https://doi.org/10.1186/s13049-016-0341-1>
- Yumoto, T., Naito, H., Yorifuji, T., Maeyama, H., Kosaki, Y., Yamamoto, H., Tsukahara, K., Osako, T., & Nakao, A. (2018). Cushing's sign and severe traumatic brain injury in children after blunt trauma: a nationwide retrospective cohort study in Japan. *BMJ Open*, 8(3), e020781. <https://doi.org/https://dx.doi.org/10.1136/bmjopen-2017-020781>