

Junpeng M, Huang S, Qin S. Progesterone for acute traumatic brain injury Review). Cochrane Database of Systematic Reviews 2011;Issue 1, Art # CD008409.

Design: Meta-analysis of randomized clinical trials

PICOS:

- **Population:** Patients with acute TBI of any severity due to head injury
- **Interventions:** Natural progesterone administered in any dose by any route within 24 hours of injury
- **Comparison:** Placebo or no progesterone
- **Outcomes:** (1) Mortality, (2) disability on any measure of neurological functioning and disability, (3) intracranial pressure
 - o Blood pressure, body temperature, and adverse events were recorded as secondary outcomes
- **Study types:** Published and unpublished randomized clinical trials of progesterone versus no progesterone for acute TBI

Study search and selection:

- Electronic searches included MEDLINE, EMBASE, LILACS (Latin American and Caribbean System on Health Sciences Information), Cochrane Central Register, clinicaltrials.gov, and controlled-trials.com
- Searches were done through April 2010
- Two authors independently assessed titles and abstracts of search citations and extracted data needed for quality of evidence
- Quality judgments were based upon assessment of the risk of bias using the *Cochrane Handbook for Systematic Reviews of Interventions*; randomization sequence generation, allocation concealment, blinding, completeness of outcome data, selective outcome reporting, and other criteria

Results:

- 3 studies, with 315 participants, were selected for meta-analysis
- Two studies were done in China and 1 in the USA
- The pooled relative risk of death was 0.61 (progesterone reduced risk of death by 39%)
 - o Even though the timing of mortality was different in the three studies (30 days, 3 months, and 6 months), the mortality estimates were fairly homogeneous
- Disability (using the Glasgow Outcome Scale) was reported by all 3 studies, but in only two studies was the GOS reported in a way that could be classified as favorable (GOS 4 or 5) or unfavorable (death or a GOS score from 1 to 3)
 - o The pooled relative risk of disability for the two studies was 0.77 (progesterone had a 23% lower risk of an unfavorable outcome)
- All 3 studies reported collecting intracranial pressure, but significant differences were not reported
- Adverse events were not common, and were rare in both progesterone and placebo groups

- One trial reported data separately for patients with moderate and severe TBI; the other two reported on only severe TBI
 - o Only 24 patients had moderate TBI; an effect of progesterone on death could not be concluded, but the risk of a bad outcome on disability in the progesterone group was 48% the risk of a bad outcome in the placebo group

Authors' conclusions:

- Progesterone may improve the neurologic outcome of patients suffering TBI
- Further evidence is still needed to support the routine use of progesterone in the management of TBI

Comments:

- Although only three studies were pooled for mortality estimates, the confidence intervals for the risk ratio (0.40 to 0.93) does exclude the null value
- Number needed to treat can be estimated from the data in Analysis 1.1; this is the inverse of the risk difference (0.11), and means that 9 patients with TBI need to be treated with progesterone to prevent one death; the forest plot is below:

Study or Subgroup	Progesterone		Control		Weight	Risk Difference M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Wright 2006	10	77	7	23	24.8%	-0.17 [-0.38, 0.03]
Xiao 2007	15	82	25	77	55.7%	-0.14 [-0.28, -0.01]
Xiao 2008	7	30	5	26	19.5%	0.04 [-0.17, 0.26]
Total (95% CI)		189		126	100.0%	-0.11 [-0.21, -0.02]
Total events	32		37			
Heterogeneity: Chi ² = 2.52, df = 2 (P = 0.28); I ² = 21%						
Test for overall effect: Z = 2.26 (P = 0.02)						

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- NNT of 9 is generally considered to be an effective intervention for preventing death
- For an unfavorable outcome (severe disability or death), the risk difference is 0.15 and NNT is between 6 and 7:

Study or Subgroup	Progesterone		Placebo		Weight	Risk Difference M-H, Fixed, 95% CI
	Events	Total	Events	Total		
Wright 2006	49	70	18	22	29.7%	-0.12 [-0.31, 0.08]
Xiao 2008	34	82	44	77	70.3%	-0.16 [-0.31, -0.00]
Total (95% CI)		152		99	100.0%	-0.15 [-0.27, -0.02]
Total events	83		62			
Heterogeneity: Chi ² = 0.10, df = 1 (P = 0.76); I ² = 0%						
Test for overall effect: Z = 2.33 (P = 0.02)						



- Although there were 32 deaths in the progesterone group, there were 83 unfavorable functional outcomes, meaning that in 51 of the 152 progesterone-treated patients, the patients survived with GOS scores of 1, 2, or 3

Assessment: will support a statement that there is some evidence that progesterone in the setting of acute TBI can reduce mortality and disability, although most patients with severe TBI may not avoid residual disability, and there is insufficient evidence to recommend progesterone for routine use.