Indian Journal of Emergency Pediatrics
Volume 3 Number 1, Jan - Mar 2011

Management of Pediatric emergencies: current evidence from Cochrane/other systematic reviews

Clinical Question 1: Which Vasoactive agent/s for Shock

Jhuma Sankar

ABSTRACT

Dopamine and dobutamine are the first line agents in septic shock as per the recommendations of the surviving sepsis campaign guidelines. In this issue we have tried to focus on the literature available on the use of these two agents either alone or in combination with other agents and have tried to come up with practical recommendations that are specific to a particular physiologic state.

Key words: Septic shock, dopamine, dobutamine

You have been called to manage a 6-month old infant who presented to the emergency department with high grade fever, vomiting, diarrhea, lethargy, poor feeding, and decreased urine output for one day. On examination, the infant appears listless and less responsive to stimuli; his vitals - HR 212/min, RR 48/min, BP 54/34 mmHg, and CFT = 5 sec; has cool peripheries with mottled extremities; central pulses weakly felt and distal pulses not palpable; systemic examination - normal.

After initial stabilization and fluid resuscitation (with 60ml/kg of crystalloids), his vitals are - HR 170/min, RR 48/min, BP 56/40mmHg, and CFT = 4 sec.

Now that the infant continues to be in decompensated shock despite optimal fluid therapy, you are required to start a vasoactive agent to improve his perfusion pressure. The questions that come to your mind at this point would be

1. Does this child require a vasopressor or inotrope or both?
2. If yes, which agent should I start with - Dopamine or Dobutamine?
3. If available, do the results favor any of these over the others?
4. Are there any guidelines for the management of septic shock with regard to use of vasoactive medications?

You decide to review the available literature for providing the best therapeutic approach for this child.

CASE SCENARIO

Clinical question 1

Is dopamine more effective than dobutamine as the first line agent in management of infants and children with septic shock?

In the first part of the series on pediatric septic shock, we had reviewed the important physiologic principles of septic shock and the importance of early goal directed therapy (EGDT). [1] In this part, let us discuss the evidence for use of various vasoactive agents in septic shock.

Author's affiliation: Department of Pediatrics, Postgraduate Institute of Medical Education and Research (PGIMER), Dr R.M.L Hospital, New Delhi.

Reprint's request: Dr. Jhuma Sankar, Department of Pediatrics, Postgraduate Institute of Medical Education and Research (PGIMER), Dr R.M.L Hospital, New Delhi.

The first step in the management of septic shock is to assess the severity of the shock - whether compensated or decompensated (based on blood pressures); in addition, it is also useful to categorize into 'cold shock' or 'warm shock' depending on the clinical parameters listed in *Table 1*.

Table 1: Clinical and Laboratory features of 'Cold shock' and 'Warm shock'

Clinical / Lab parameters	Cold shock	Warm shock
1. **Tachycardia**	Present	Present
2. **Pulses**	Feeble	Bounding
3. **Blood pressure**	Normal or decreased (in late stages)	Normal or decreased (in late stages) with wide pulse pressure
4. **Peripheries**	Cool, mottled	Warm
5. **Capillary refill time (CRT)**	>2 seconds	Flush, ≤2 seconds
6. **Sensorium**	Altered	Altered
7. **Urine Output**	Decreased	Decreased
8. **Mixed venous saturation (Scvo2)**	<70%	Usually > 70%
9. **Lactate / base deficit**	Increased	Increased

Whatever the physiological state of shock, if left untreated, the end result is decreased tissue oxygenation resulting in cell death. However, different physiologic states of shock require administration of different vasoactive agent/s for optimal effect and often the reason for non-improvement or refractory shock is the inappropriate use of these agents. The various agents available according to their principal mechanism of action and the indications for use of these agents has already been discussed in the previous issue.[1]

For the purpose of this series, we would be restricting our discussion to use of inotropes/ vasopressor in shock and evidence supporting or refuting the same. In this issue, the evidence for choosing the appropriate first line agent for shock - dopamine versus dobutamine - will be discussed. In the subsequent series, we would be looking at evidence comparing the second line agents i.e. epinephrine, nor-epinephrine, phosphodiesterase inhibitors, and vasodilators in combination or individually. Since we plan to discuss the management of septic shock in neonates separately, we have not reviewed the evidence in them.

DOPAMINE / DOBUTAMINE

Evidence

We searched the Cochrane database of systematic reviews. Till date, there is only one Cochrane review on the use of vasopressors in shock - by Mullner et al. [2]

The objectives of the review were (a) to identify whether particular vasoactive agents were more effective in reducing the overall mortality and (b) to evaluate if the choice of vasopressor had an impact on the length of ICU stay and quality of life.

Methodology

Blinded and unblinded RCTs comparing various vasopressors, vasopressors with placebo and vasopressors with intravenous fluids for the treatment of any kind of shock were included in the review. Only studies with patient oriented outcomes such as mortality were included.

Results

Eight randomized controlled trials mostly comprising adult patients were included. The

methodological quality of many items reported was unsatisfactory according to the authors. Only two RCTs reported allocation concealment, and two other studies reported that the outcome assessor was blinded to the intervention.

Unfortunately, none of the studies have compared dopamine with dobutamine.

Conclusion

The authors concluded that the current available evidence *was not suited to be incorporated into clinical practice and it was not possible to comment on whether a particular vasopressor was superior to another in the management of shock at this time point*. Large multicentre trials with pragmatic study protocols would be required to answer these questions.

Other systematic reviews: No other systemic reviews were found in children comparing dopamine versus dobutamine as the first line agent. However a number of clinical studies/ animal experiments have been reported on the effects/ use of these agents alone or in combination, the findings of which are summarized below (see table 2).

Table 2: Summary of studies comparing Dopamine/Dobutamine

	Author	Setting	N	Methods	Results	Conclusion
1995	Hanneman et al [3]	Postoperative, hyperdynamic septic shock patients.	25	Prospective study of two patient groups to see whether dopamine infusion improved oxygen delivery (Do2) and oxygen uptake (VO2) in patients stabilized by fluids and dobutamine alone, or by a combination of dobutamine and norepinephrine. Group 1(n = 15) was given dobutamine, and group 2 (n = 10) was given dobutamine plus norepinephrine. The stabilizing catecholamine infusion was replaced in a stepwise manner by dopamine to achieve a similar MAP	The change to dopamine infusion resulted in higher cardiac index [cardiac index (group 1: 20% [p < .01]; group 2: 33% [p < .01])]and DO2 (group 1: 19% [p < .01]; group 2: 27% [p < .01]) values in patients stabilized on dobutamine alone but not the VO2 values. The O2ER also decreased with the use of dopamine. Heart rate, pulmonary artery occlusion pressure, and pulmonary shunt fraction increased with dopamine.	Short-term dopamine infusion in hyperdynamic septic shock patients, despite producing higher global DO2, was not superior to dobutamine or the combination of dobutamine and norepinephrine infusion
2002	Yang Y et al [4]	Sheep with lipopolysccharide induced septic shock	20	RCT comparing the effect of norepinephrine-dobutamine with dopamine alone on splanchnic perfusion in sheep with septic shock. Each group was randomized to receive an intravenous infusion of norepinephrine-dobutamine or dopamine titrated to maintain mean arterial pressure (MAP) > 12 kPa with an optimal preload.	MAP, cardiac output, and oxygen delivery increased in all animals compared with basic values in both groups (P < 0.05). Lactate concentrations decreased at 3 h and 4 h [from (4 +/- 2) mmol/L to (2 +/- 1) mmol/L] in the norepinephrine-dobutamine group (P < 0.05) and arterial pH decreased from 7.40 +/- 0.05 to 7.26 +/- 0.06 at 1 h (P < 0.05) in the dopamine group with no change in the lactate values. No difference in splanchnic circulation pH was found in dopamine group, but in the norepinephrine-dobutamine group, compared to baseline, pHi increased from 7.19 +/- 0.04 to 7.36 +/- 0.07 at 3 h (P <0.05)	Combination of norepinephrine-dobutamine or dopamine alone could improve systemic hemodynamics in sheep with septic shock, but the former combination was better than dopamine on splanchnic perfusion.

Having reviewed the limited evidence available comparing the two agents the following recommendations can be made:

1. In a child with septic shock, the first line vasoactive agent can be either dopamine or dobutamine depending on the pathophysiology as per the recommendations of the surviving sepsis campaign guidelines. [5]
2. If a child has evidence of fluid refractory shock with low blood pressures, dopamine should be started as the first line agent at a dose of 10 microgram/kg/min and subsequently titrated to achieve the desired effect. If despite improvement in the blood pressures the perfusion remains poor or there is evidence of decreased oxygen delivery/extraction measured by the $ScvO_2$, dobutamine should be added.
3. A child having features of cold shock with normal blood pressure should preferably be started on dobutamine infusion at a dose of 10 microgram/kg/min and then titrated to achieve the desired effect. If on starting dobutamine infusions the blood pressures fall, then dopamine infusion should be started along with fluid boluses.
4. If a child continues to be in shock despite maximal doses of these drugs, second line agents such as epinephrine/ nor epinephrine/milrinone should be considered.[5]

Applying evidence to practice

The child should be started on dopamine infusion and monitored to see the effect of therapy and for any worsening of symptoms. It would be advisable to get a ScvO2 in this case as it will guide us in further deciding the agents/course of action. Both dopamine and dobutamine have similar efficacy in improving the oxygen deliver y, however we need to choose the agent depending on the evidence of systemic vascular resistance and the cardiac output of the child.

In our subsequent series we would be reviewing the evidence for use of the second line agents and we would also be looking at shock in neonates; how different/similar it is to pediatric septic shock and the management of the same.

REFERENCES

1. Sankar J. Management of pediatric emergencies: Septic shock. Indian Journal of Emergency Pediatrics. 2010; 2: 141-50.
2. Müllner M, Urbanek B, Havel C, Losert H, Waechter F, Gamper G. Vasopressors for shock. Cochrane Database Syst Rev. 2004; 3: CD003709.
3. Hannemann L, Reinhart K, Grenzer O, Meier-Hellmann A, Bredle DL. Comparison of dopamine to dobutamine and norepinephrine for oxygen delivery and uptake in septic shock. Crit Care Med. 1995; 23: 1962-70.
4. Yang Y, Qiu HB, Zhou SX, Tan Y, Li SQ. Comparison of norepinephrine-dobutamine to dopamine alone for splanchnic perfusion in sheep with septic shock. Acta Pharmacol Sin. 2002; 23: 133-7.
5. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008.Crit Care Med. 2008; 36: 296-327.