



---

# Haemodynamics During Endotoxic Shock and after I/V Infusion of a Combination of NSAIDs in Buffalo Calves

**Corresponding Author:**

Dr. Digvijay Singh,  
Professor, Dept of Veterinary Physiology and Biochemistry, C.O.V.S., GADVASU, 141004 - India

**Submitting Author:**

Dr. Digvijay Singh,  
Professor, Dept of Veterinary Physiology and Biochemistry, C.O.V.S., GADVASU, 141004 - India

**Article ID:** WMC001944

**Article Type:** Research articles

**Submitted on:** 30-Nov-2011, 06:26:45 AM GMT **Published on:** 30-Nov-2011, 09:39:51 AM GMT

**Article URL:** [http://www.webmedcentral.com/article\\_view/1944](http://www.webmedcentral.com/article_view/1944)

**Subject Categories:** MEDICINE

**Keywords:** Buffalo calves, Flunixin meglumine, Ketanov, Haemodynamics, Endotoxic shock, NSAIDs.

**How to cite the article:** Singh D , Bansal S K. Haemodynamics During Endotoxic Shock and after I/V Infusion of a Combination of NSAIDs in Buffalo Calves . WebmedCentral MEDICINE 2011;2(11):WMC001944

**Source(s) of Funding:**

GADVASU

**Competing Interests:**

None

# Haemodynamics During Endotoxic Shock and after I/V Infusion of a Combination of NSAIDs in Buffalo Calves

**Author(s):** Singh D , Bansal S K

## Abstract

Endotoxemia is potentially damaging complication of several diseases of cattle and buffaloes like following urinary tract infections (UTI), intesusception, peritonitis, septicemia, caeserian section, metritis, mastitis and dystocia due to maceration. To investigate the effect of Flunixin meglumine and Ketorolac tromethamine (Ketonov) a combination of NSAIDs; on endotoxemic buffalo calves, five apparently healthy male buffalo calves aged between 6-8 month were subjected to i.v. infusion of *E. coli* endotoxin @ 5µg/Kg/ BW/hour for 3 hours. The endotoxin infusion lead to the development of clinical symptoms of restlessness, respiratory distress characterized by labored and abdominal respiration, diarrhea and profuse salivation. The animals closed their eyes and struggled intermittently with the progression of the endotoxin infusion. A highly significant ( $P < 0.01$ ) fall in mean systolic, diastolic, pulse, mean arterial pressure (MAP.) ,Central Venous pressure (C.V.P.) and hemoglobin was observed till the end of endotoxin infusion while respiratory rate was significantly elevated along with a non-significant alteration in rectal temperature and hematocrit during the infusion of endotoxin. Immediately at the end of endotoxin infusion, Flunixin meglumine was injected through the jugular vein @ 1 .1 mg/KgBW followed by Ketorolac tromethamine @ 1.1 mg/kgBW. The infusion of both these NSAIDs resulted in increase in systolic, diastolic, pulse, central venous pressure close to pre-infusion normal level while mean arterial pressure (MAP) was higher than normal pre-infusion values at 300 and 420 minute. The respiratory rate was elevated throughout the observation period even consequent to flunixin meglumine and Ketorolac tromethamine administration. All the animals opened their eyes and were alert. This drug combination successfully restored the various hemodynamic parameters to normal pre-infusion values and can be used to provide immediate relief to the endotoxemic buffalo calves thus allowing clinician valuable time to plan further long term treatment.

**Keywords:** Buffalo calves, Flunixin meglumine, ketonov, haemodynamics, endotoxic shock.

## Introduction

Endotoxemia is a potentially devastating complication of several diseases of cattle e.g. enteric disease, septicemia, metritis, mastitis and pneumonia. (Semrad ,1993a).After gaining access to the circulation, endotoxin causes a variety of adverse effects including cardiovascular compromise, lactic acidosis, leukopenia, glucose dyshomeostasis, hemostatic alteration, gastrointestinal, respiratory and renal disturbances. Endotoxemia is a life threatening inflammatory condition which can lead to shock, multiple organ failure, suppression of immune system and wound healing processes (Ng et al 2008) The traditional treatment for endotoxemic animals attempts to support cardiac and pulmonary function, eliminate causative microbes and modulate the production of endogenous mediators. Non steroidal anti inflammatory drugs are beneficial in the management of endotoxemia.

Flunixin meglumine is a cyclo-oxygenase inhibitor and prevents the formation of prostaglandins, responsible for inflammatory response (Goodwin and Schaer 1989, Kopcha et. al.,1989).

Ketorolac tromethamine, a pyrrolo-pyrrole NSAID is used in human medicine to relieve postoperative and musculoskeletal pain (Semrad, 1993 b) while Flunixin meglumine , an aminonicotinic acid NSAID is used to treat endotoxemia in horses and cattle because it effectively suppresses clinical abnormalities, early haemodynamic alterations, biochemical changes and eicosanoid production associated with challenge exposure to endotoxin. According to Semrad et.al.,(1993) the benefits of simultaneous administration of 2 NSAIDs over administration of a single drug at higher doses are not known however if one agent has a good central analgesic activity and the other is a more effective anti-inflammatory agent, clinical efficacy may be enhanced.

In view of the above, the present investigation was carried out to elucidate the effects of flunixin meglumine and ketonov (ketorolac tromethamine) in combination to know if there was any synergistic effect of these two NSAIDs on hemodynamics of endotoxemic buffalo calves.

## Materials and methods

Normal healthy male buffalo calves (5), aged between 6-8 months with body weight range 70-110 kg procured from local market were dewormed a week before the experiment with fenbendazol @ 5 mg/kg B.W. The E-coli endotoxin (lyophilized, phenol extracted O111:B4 lipopolysaccharide, SIGMA chemicals, USA) was reconstituted by dissolving it in 0.9% normal saline to make a stock-solution of 1 mg/ml. Endotoxin concentration of 5 µg/ml was prepared by dissolving 1 ml of stock solution in 199 ml of normal saline. Endotoxin was I/v infused in the animals @ 5 µg 1 kg BW/ hr for 3 hrs followed immediately with infusion of flunixin meglumine @ 1.1 mg/kg BW and ketorolac tromethamine @ 1.1 mg/ kg BW.

The animals were casted in right lateral recumbency on the operation table. Before endotoxin infusion, an area over the jugular furrow was shaved and disinfected with savlon. The local anaesthetic lignocaine (2%) 90 ml was injected sub-cutaneous and intramuscularly before catheterization of the carotid artery and jugular vein to alleviate pain. The skin was incised to expose and catheterize the carotid artery and jugular vein. Siliconized polyethylene catheter was inserted into the carotid artery and was connected to mercury manometer through a 3-way cannula with stop cork for the record of arterial blood pressure. The jugular vein was catheterized and attached to the saline manometer (Ramson's scientific and surgical India Pvt. Ltd, Agra-India) for the record of CVP and administration of endotoxin and flunixin meglumine.

Packed cell volume was estimated by microhaematocrit method while Hb was measured by cyanmethaemoglobin method by the use of spectrophotometer by colorimetric method at 540 nm (Dacie and Lewis, 1975). Body temperature was recorded by using standard clinical thermometer from the rectum of the animal. Thermometer was in touch with the mucosa for one minute during every observation.

The data were pooled and analyzed using Randomized Design ANOVA and T-test (Snedecor and Cochran 1976). All the values obtained were compared with the normal pre-infusion values.

## Results and Discussions

The I.V. infusion of endotoxin in animals led to the development of clinical symptoms of restlessness,

respiratory distress characterized by labored and abdominal respiration, diarrhea and profuse salivation. The animals closed their eyes and struggled intermittently with the progression of endotoxin infusion.

The normal mean systolic pressure was observed to be 132.40±6.05mmHg (table 1). The mean systolic pressure decreased significantly after endotoxin infusion. An increase in systolic pressure was seen on treatment with flunixin meglumine (FM) and ketonov and it remained non-significantly below the normal values (Table-1). Similar results have been reported by Singh et al (2005).

The normal mean diastolic pressure was 90.8± 6.65 mmHg (Table 1) which is slightly lower than the normal range of 118.0±7.80 to 122.40±7.41 mmHg as reported by Singh et al., 2002. The diastolic pressure was significantly (P) The normal MAP (Mean arterial pressure) was found to be 104.66±5.97 (table 1) which is lower than 130.00±6.4 mm Hg (Singh et al 2005) and 153.88±2.00 mmHg (Singh 1997). The fall in MAP throughout endotoxin infusion was significant and after infusion of Flunixin meglumine and ketonov, it was slightly higher than the normal value at the end of the experiment (table 1). The fall in MAP during endotoxin infusion may be due to the release of 6-Keto prostaglandin-F- $\alpha_2$  (Margolis et al 1987). The rise in MAP after Flunixin meglumine may be due to the fact that NSAIDs like flunixin meglumine, Ketoprofen and Ketorolac are cyclo oxygenase inhibitor and prevents the formation of prostaglandin and hence improves tissue perfusion (Semred 1993).

The normal CVP was 4.40±0.66 cm (table 1) which is lower than 8.30±1.67 cm (Sobbi et al 1981), 0.10±0.46 cm (Singh et. Al 1979, 2005). There was a significant fall in CVP throughout endotoxin infusion from 60 min to 180 min (table 1). The fall in CVP may be due to peripheral pooling of blood (Singh et al 2005). According to Singh (1979) failure of capacitance changes due to lack of venous constriction contributes to reduction in CVP. After Flunixin meglumine and ketonov, CVP showed a marked increase at 4 hour (table 1) and its level was non-significantly lower than the pre-infusion value.

The normal respiration rate was 8.20±0.73 movt./min (table 1) which is close to 7.20±0.47 to 9.20±1.36 movt/min as reported by Singh et al (2002). Under the influence of endotoxin, the respiration rate increased and its value was significantly higher than the normal at 7th hour (table 1). Similar effect of endotoxin on respiration rate has earlier been reported in mature cattle and cow calves (Semrad 1993, Dupe et al 1993).

The normal body temperature was observed to be

99.20±0.68 °F (table 1) which is slightly lower than 102.2 °F as reported by Constable et al (1996). There was a non-significant decrease in body temperature with in normal range during endotoxin infusion and after treatment with Flunixin meglumine and ketonov. The normal PCV was found to be 30.40±1.54 % (table 1) which was similar to 29.0±4.0 % to 35.0±6.0 % (Constable et al 1996) but slightly higher than 27.20±3.40 % (Singh 1979). Significant decrease in PCV was seen during endotoxin infusion and after infusion of Flunixin meglumine and ketonov (table 1).

The normal haemoglobin was 10.60±0.48 g% (Table 1) which is close to 9.5±1.30 to 11.40±1.80 g % (Constable et al 1996) and 10.44±0.36 to 11.40±0.38 g % (Singh et al 2005). The mean Hb level showed a non-significant decrease during endotoxin infusion. After Flunixin Meglumine and ketanov infusion, the Hb values were recorded to be close to normal value (Table 1).

All the animals opened their eyes and were alert. This treatment not only successfully raised systolic, diastolic, pulse and mean arterial pressure to normal pre-infusion value but alleviated the clinical symptoms developed due to endotoxin infusion observed earlier.

This combination of Flunixin meglumine and Ketanov offered only one additional specific advantage in comparison to administration of flunixin meglumine alone in endotoxemic buffalo calves which was the significantly higher diastolic pressure as compared to non-significant alterations in diastolic pressure of endotoxemic buffalo calves infused with flunixin meglumine alone (table-2). In general, the administration of two NSAIDs in combination confers no advantage over higher doses of a single drug. (Merck's Veterinary Manual 2008.)

From the results of the present investigation, it can be concluded that I.V. infusion of Flunixin meglumine in endotoxemic buffalo calves effectively restores the various hemodynamic parameters to normal pre-infusion values and it can be used as immediate resuscitation measure to provide the clinician valuable time to plan further long term treatment.

## References

1. Constable P D, Gohar H M, Morin D E and Thurmon J C (1996). Use of hypertonic saline- dextrin solution to resuscitate hypovolemic calves with diarrhoea. *American Journal of Veterinary Research* 57(1): 97-104
2. Dacie J V and Lewis S M (1975) *Practical hematology*, PP32, Churchill and Livingstone V. Edu.
3. Dupe R, Bywater RJ and Goddard M (1993) A

hypertonic infusion in the treatment of experimental shock in calves and clinical shock in dogs and cats. *Veterinary Record* 133: 585-590.

4. Goodwin JK and Schaer M (1989) Septic shock. *Veterinary clinics of North America* 19(6): 1239-58.
5. Kopcha M and Ahl A S (1989). Experimental use of flunixin meglumine and phenyl butazone in food producing animals: *Journal of American Veterinary Research Communications* 11(5): 479-91
6. Margolis J H, Buttons G D and Fessler J F (1987). The efficacy of Dexamethasone and Flunixin meglumine in treating endotoxin induced changes in calf. *Veterinary Research Communications* 11(5): 479-91.
7. *The Merck's Veterinary Manual*, 8th Edition. PP1824. Merck and Company Incorporate, White House station, New Jersey, U.S.A.
8. Ng SW, Zhang H, Hedge A and Bhatia M. 2008. Role of preprotachykinin-A gene products on multiple organ injury in LPS- induced endotoxemia. *Journal of leucocyte Biology* 83: 288-95.
9. Semrad SD (1993a) Comparison of Flunixin, Prednisolone, Dimethyl sulphoxide and a lazaroid for treating endotoxemic neonatal calves. *American Journal of Veterinary Research* 54 (8): 1339-46.
10. Semrad SD (1993b) Comparative efficacy of flunixin, ketoprofen and Ketorolac for treating endotoxemic neonatal calves. *American Journal of Veterinary Research* 54 (9): 1511-16.
11. Semrad SD, Sams RA, Harris O N and Ashcraft S M (1993) Effects of concurrent administration of phenyl butazone and flunixin meglumine on pharmacokinetic variables and invitro generation of thromboxane B2 in mares. *American Journal of Veterinary Research* 54 (11): 1901-05.
12. Singh J (1979). An investigation into Patho-Physiology and treatment of shock in bovines, Ph.D. dissertation, Punjab Agricultural University, Ludhiana, India.
13. Singh K, Krishnamurthy D and Peskin P K (1997). Endotoxin shock with and without dexamethasone pre-treatment in anaesthetized buffalo calves. II. *Indian Journal of Veterinary Surgery* 18 (1): 8-11.
14. Singh D V, Singh R V and Sodhi S P S (2002). Effect of HSS on haemodynamics of endotoxemic buffalo calves. *Indian Journal of Animal Sciences* 72 (12): 1083-86.
15. Singh D V, Singh R V and Sodhi S P S (2005). Effect of blood transfusion in combination with Dextran-40 and hypertonic Saline Solution on cardiopulmonary haemodynamics of endotoxic shock in buffalo calves. *Veterinary Research Communication* 29 (5): 421-30.
16. Snedecor GW and Cochran WG(1976) *Statistical*

methods. Iowa State College Printing Press, Iowa  
USA.

## Illustrations

### Illustration 1

Table 1: Some haemodynamic parameters during bovine endotoxic shock and after i/v infusion with Flunixin meglumine Ketonov.

Parameter	Normal	60 Min	120 Min	180 Min	240 Min	300 Min	360 Min	420 Min
Systolic Pressure (mmHg.)	132.40 ± 6.05	<b>96.40</b> ± <b>5.15*</b>	<b>84.80</b> ± <b>6.34*</b>	<b>93.60</b> ± <b>5.42*</b>	122.80 ± 4.80	124.80 ± 1.36	126.00 ± 3.74	129.60 ± 5.04
Diastolic Pressure (mmHg.)	90.80 ± 6.65	<b>68.40</b> ± <b>5.23*</b>	<b>67.40</b> ± <b>6.24*</b>	<b>69.60</b> ± <b>5.49*</b>	85.60 ± 4.35	96.80 ± 1.96	92.00 ± 3.74	<b>107.20</b> ± <b>5.08*</b>
Pulse Pressure (mmHg.)	26.80 ± 13.40	28.40 ± 14.20	<b>18.00</b> ± <b>2.53*</b>	25.60 ± 4.12	37.20 ± 4.27	28.00 ± 2.61	34.00 ± 4.00	22.40 ± 1.94
Mean Arterial Pressure (mmHg.)	104.66 ± 5.97	<b>77.20</b> ± <b>4.56*</b>	<b>73.60</b> ± <b>6.23*</b>	<b>78.13</b> ± <b>4.94*</b>	98.00 ± 4.03	106.13 ± 1.29	103.33 ± 3.23	114.67 ± 4.98
Central Venous Pressure (mm Sae)	4.40 ± 0.66	<b>1.30</b> ± <b>0.70*</b>	<b>-0.10</b> ± <b>0.93*</b>	<b>-2.60</b> ± <b>0.60*</b>	3.90 ± 0.58	4.30 ± 0.68	3.20 ± 0.46	<b>0.80</b> ± <b>1.05*</b>
Respiration (per minute)	8.20 ± 0.73	11.20 ± 0.97	<b>14.00</b> ± <b>1.14*</b>	<b>16.00</b> ± <b>2.02*</b>	<b>14.40</b> ± <b>2.38*</b>	<b>15.20</b> ± <b>1.83*</b>	<b>14.60</b> ± <b>1.89*</b>	<b>16.00</b> ± <b>1.41*</b>
Heamatocrit (%)	30.40 ± 1.54	29.00 ± 1.38	27.40 ± 1.29	<b>26.40</b> ± <b>0.93*</b>	<b>26.60</b> ± <b>0.93*</b>	<b>26.60</b> ± <b>1.03*</b>	<b>26.40</b> ± <b>0.81*</b>	<b>26.60</b> ± <b>1.03*</b>
Haemoglobin (%)	10.60 ± 0.48	10.39 ± 0.49	10.08 ± 0.42	9.79 ± 0.37	9.83 ± 0.38	9.90 ± 0.36	9.78 ± 0.40	9.87 ± 0.40
Rectal Temperature (° F)	99.20 ± 0.68	99.48 ± 0.74	99.84 ± 0.80	100.20 ± 0.81	100.16 ± 0.73	100.24 ± 0.66	100.40 ± 0.55	100.28 ± 0.57

\* Significant at 5% level. No. of animals = 5

## Illustration 2

Table 2: Different haemodynamic parameters at different stages of endotoxic shock and after treatment with flunixin meglumine.

Parameter	<i>Endotoxic Shock</i>			<i>After Treatment</i>				
	0 hr	1 hr	2 hr	3 hr	4 hr	5 hr	6 hr	7 hr
Systolic pressure (mmHg)	161.20 ± 11.36	<b>122.80 *</b> ± <b>11.02</b>	<b>123.60 *</b> ± <b>2.79</b>	<b>111.60 * ± 3.49</b>	154.00 ± 9.01	158.40 ± 7.76	157.20 ± 7.63	155.60 ± 7.93
Diastolic pressure (mmHg)	124.00 ± 13.18	98.00 ± 14.94	100.00 ± 8.17	<b>93.20*</b> ± <b>5.08</b>	122.40 ± 4.80	129.20 ± 8.64	132.40 ± 10.17	126.40 ± 12.02
Pulse pressure (mmHg)	35.20 ± 5.60	24.80 ± 5.82	23.60 ± 6.11	<b>18.40*</b> ± <b>3.54</b>	31.60 ± 4.12	29.20 ± 4.22	24.80 ± 3.93	29.20 ± 6.56
Mean Arterial pressure (mmHg)	135.73 ± 12.02	<b>106.26 *</b> ± <b>13.48</b>	<b>107.86 *</b> ± <b>6.23</b>	<b>101.33* ± 5.34</b>	132.93 ± 8.04	139.06 ± 0.10	140.66 ± 9.21	136.13 ± 10.38
Central venous pressure (Cm)	3.10 ± 0.93	<b>-0.90 *</b> ± <b>1.25</b>	<b>-0.70 *</b> ± <b>1.41</b>	<b>-0.20*</b> ± <b>1.98</b>	4.50 ± 1.06	2.80 ± 1.59	1.50 ± 1.48	-0.60 ± 1.36
Respiration rate (movt/min)	11.80 ± 1.20	10.20 ± 1.74	<b>21.40 *</b> ± <b>2.46</b>	<b>21.00*</b> ± <b>1.61</b>	14.80 ± 1.16	14.80 ± 1.50	14.60 ± 1.86	14.60 ± 1.43
Body temperature (°F)	100.88 ± 0.69	100.32 ± 0.95	100.72 ± 0.99	100.76 ± 0.97	100.32 ± 0.83	100.18 ± 0.75	100.22 ± 0.80	100.32 ± 0.72
Hemato crit (PCV) (%)	35.20 ± 1.43	34.20 ± 1.20	33.00 ± 1.14	32.20 ± 1.24	33.40 ± 1.29	33.80 ± 0.97	33.40 ± 1.17	33.80 ± 1.07
Hemoglobin (g/dl)	12.51 ± 0.28	12.19 ± 0.25	11.87 ± 0.24	<b>11.57 *</b> ± <b>0.18</b>	11.97 ± 0.14	12.36 ± 0.20	11.97 ± 0.10	12.01 ± 0.08

\*Significant at 1% level

No. of animals = 5

## Disclaimer

This article has been downloaded from WebmedCentral. With our unique author driven post publication peer review, contents posted on this web portal do not undergo any prepublication peer or editorial review. It is completely the responsibility of the authors to ensure not only scientific and ethical standards of the manuscript but also its grammatical accuracy. Authors must ensure that they obtain all the necessary permissions before submitting any information that requires obtaining a consent or approval from a third party. Authors should also ensure not to submit any information which they do not have the copyright of or of which they have transferred the copyrights to a third party.

Contents on WebmedCentral are purely for biomedical researchers and scientists. They are not meant to cater to the needs of an individual patient. The web portal or any content(s) therein is neither designed to support, nor replace, the relationship that exists between a patient/site visitor and his/her physician. Your use of the WebmedCentral site and its contents is entirely at your own risk. We do not take any responsibility for any harm that you may suffer or inflict on a third person by following the contents of this website.