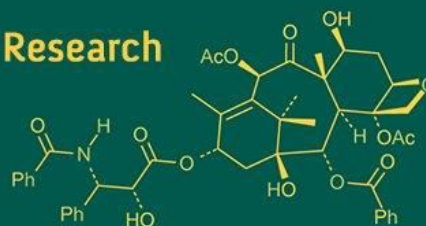


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Comparative clinical evaluation of total intravenous anaesthesia with xylazine-ketamine-guaifenesin and dexmedetomidine-ketamine-guaifenesin in horses

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Abstract

Background: In India, horses undergoing several surgical procedures that need for safe anaesthetic procedures. For short-term treatments, Total Intravenous Anaesthesia (TIVA) provides several advantages over inhalants. This study evaluates and compares xylazine and dexmedetomidine based TIVA protocols to improve anaesthetic safety, efficacy and recovery quality in equine surgeries, addressing the challenges of equine anaesthetic management.

Methods: The study assessed two distinct combinations of total intravenous anaesthesia (TIVA) in horses for anaesthetic parameters, including induction, time and quality of sedation and recovery. The study was a prospective, randomised clinical trial with two groups of six horses each and 12 clinical cases of horses. Acepromazine was administered to the horses as a premedication first. Twenty minutes later, the XKG group received intravenous xylazine and butorphanol, while the DKG group received dexmedetomidine and butorphanol. Xylazine-ketamine-guaifenesin (XKG) or dexmedetomidine-ketamine-guaifenesin (DKG) infusion at a steady rate (1-3 mL/kg/hr) was administered to both groups after ketamine induction. Evaluation of parameters such as time of sedation, quality of sedation, time to induction of anaesthesia, quality of induction, duration of anaesthesia, degree of muscle relaxation, and time and quality of recovery was performed and compared between the groups. Various clinico-physiological parameters, such as heart rate (HR), respiration rate (RR), rectal temperature (RT) and oxygen haemoglobin saturation in the blood (SpO₂).

Result: The results showed that, compared to the XKG group, the DKG group experienced shorter and more satisfactory sedation and induction times, a shorter recovery period, better quality of recovery and improved cardiopulmonary stability. Both drug combinations proved effective in maintaining anaesthesia during short-term procedures, with good to excellent recovery. These findings support the usage of TIVA protocols based on dexmedetomidine as a viable approach in future to enhance anaesthetic management in equine practices.

Keywords: Acepromazine, dexmedetomidine, guaifenesin, ketamine, TIVA and xylazine

Introduction

Equine anaesthesia has always been associated with greater patient risk compared to other common domestic species. The main challenge in equine anaesthesia, compared to other domestic animals, is ensuring the safe return of the horse to a standing position without injury. The anaesthetist's role extends into recovery, involving the choice of suitable sedatives and regularly assisting the horse as it tries to stand (Bidwell 2015) [4]. Balanced anaesthesia ensures stable cardiopulmonary function during surgery, reduces pain and promotes calmer, smoother and more coordinated recoveries (Bettschart-Wolfensberger and Larenza 2007) [2]. In recent years, continuous total intravenous anaesthesia (TIVA) has gained popularity in veterinary anaesthesia.

TIVA is a technique that relies entirely on intravenous anaesthetic drugs to sustain an adequate level of anaesthesia for the required degree of central nervous system depression. (Waelbers *et al.* 2009, Suarez *et al.* 2012) [27, 23]. TIVA uses a combination of an α -2 agonist with guaifenesin and ketamine, which anaesthetises animals through central nervous system (CNS) depression, muscular relaxation, and analgesia. The advantages of TIVA compared to using inhalation agents include less cardiopulmonary depression and smoother recovery, it requires less in terms of anaesthetic machine and associated equipment.

TIVA is the sole viable option for general anaesthesia in horses since, it has been found to have various potential benefits over inhalation anaesthetics, including superior cardiovascular and respiratory function maintenance, as well as a quiet and coordinated recovery (Agivale *et al.* 2019) [1]. Various ketamine-based TIVA techniques have been used, with the most common in horses being the combination of guaifenesin, ketamine and an α -2 adrenoceptor agonist, usually xylazine, detomidine or romifidine, referred to as the "Triple Drip".

There is limited clinical data on using the α -2 agonist dexmedetomidine as a premedicant and with triple drip maintenance anaesthesia in horses. This study aimed to compare the effectiveness of xylazine and dexmedetomidine in various surgical cases involving horses.

Materials and Methods

The present clinical study was conducted during 2022-2023 at the Department of Veterinary Surgery Radiology, College of Veterinary Science and Animal Husbandry, Kamdhenu University, Junagadh, Gujarat. The study involved a total of twelve horses presented for various surgical conditions, including reproductive surgeries, tenorrhaphy, minor orthopedic procedures, and elective surgeries. The animals were randomly divided into two groups, each comprising six animals. All the animals received tetanus toxoid vaccination preoperatively, were kept fasting for approximately 24 hours and water deprivation for 12 hours. A preoperative assessment of clinico-physiological and haematological parameters was conducted to evaluate their suitability for surgery. The American Society of Anaesthesiologists (ASA) classification (Kalchofner *et al.*, 2009) [13] was employed to categorise the health status of the horses following the surgical interventions that required general anaesthesia.

In Group I (XKG), premedication was administered intravenously using acepromazine (0.02 mg/kg/b.wt), xylazine (0.5 mg/kg/b.wt), and butorphanol (0.02 mg/kg/b.wt), followed by induction with ketamine (2.2 mg/kg/b.wt). Anaesthesia was maintained through total intravenous anaesthesia (TIVA) comprising xylazine (0.5 mg/mL), ketamine (2 mg/mL), and guaifenesin (50 mg/mL), delivered via continuous rate infusion (CRI) at dosages of 1-3 mL/kg/b.wt intravenously. Conversely, in Group II (DKG), premedication involved the intravenous administration of acepromazine (0.02 mg/kg/b.wt) and dexmedetomidine (3.5 μ g/kg/b.wt). ketamine (2.2 mg/kg/b.wt) was used for induction, with anaesthesia maintained using TIVA consisting of dexmedetomidine (0.5 μ g/mL), ketamine (2 mg/mL), and guaifenesin (50 mg/mL), administered as CRI at doses of 1-3 mL/kg/b.wt intravenously.

Anaesthetic parameters

The time and quality of sedation, induction and recovery were calculated (Table 1 and 2). The depth of anaesthesia (light or deep) was analysed by recording different reflexes (palpebral, corneal, photopupillary and swallowing) and the extent of muscle relaxation (relaxation of neck, jaws, tail and anal sphincter Table 3). Analgesia (using the pin prick method to test the response to noxious stimuli on the coronary band of the front and hind limbs, the shoulders and the gaskin) was interpreted as a response and a score was given ranging from 0 to 3 (Nanda *et al.*, 2014) [17] (Table 4). A score ranging from 1 to 5 according to the method of

Ringer *et al.* (2007) [20], was used to assess the quality of recovery from anaesthesia (Table 5).

Physiological Parameters

Heart rate, respiratory rate and rectal temperature were recorded. Respiration rate was recorded by observing costoabdominal movements manually and by vital signs monitor (Veterinary Monitor, NT3B-V, Solaris Medical Technology, San Francisco, USA), heart rate by auscultation and vital sign monitor, and gingival perfusion time and SpO₂ by tongue transducer attached to vital sign monitor.

The difference between the two data sets between groups were statistically analysed by using student 't' test (parametric data) and mann whitney test (non parametric data). The differences between more than two data sets within group were statistically analysed by one way ANOVA followed by using Duncan's Multiple Range Test (DMRT) using SPSS software version 20.0 (Snedecor and Cochran 1980) [22].

Table 1: Scorecard of sedation parameters.

Parameter	Score	Description
Sedation score	1 (Profound)	Animal stuporous, CTG <60 cm, severe ataxia
	2 (Strong)	Animal apathetic, CTG 60 to 80 cm, moderate ataxia
	3 (Moderate)	Animal calm, head lowered between CTG 80 to 100 cm, mild ataxia
	4 (Mild)	Animal calm, CTG >100 cm, minimal ataxia
	5 (Absent)	No apparent sedation
Response to tactile stimulation (picking the neck)	1 (Absent)	No response
	2 (Mild)	Slow, delayed response
	3 (Moderate)	Moderate response
Response to auditory stimulation (Clapping hands)	1 (Absent)	No response
	2 (Mild)	Slow, delayed response
	3 (Moderate)	Moderate response
	4 (Strong)	Rapid marked response

Table 2: Scorecard of quality of induction

Score	Quality	Character
1	Excellent	Sinks smoothly to the ground, no forward-backward movement, no excitement
2	Good	Sinks smoothly to the ground, slight forward-backward movement, slight head or limb twitching
3	Moderate	Inadequate relaxation, forward-backward movement, visible ataxia, twitching, slight limb paddling
4	Poor	Inadequate relaxation, considerable movement and ataxia, marked limb paddling
5	Very poor	Failure to reach recumbency

Table 3: Scorecard of quality of muscle relaxation

Score	Quality	Character
4	Excellent	Complete relaxation
3	Good	Adequate muscle relaxation of surgical procedure
2	Moderate	Partial relaxation of head, neck and limb muscles
1	Poor	Rigidity in muscles of neck, head and limbs.

Table 4: Scorecard for quality of analgesia

Score	Quality	Character
0	Excellent	No response
1	Good	Response to stimuli, nystagmus created
2	Moderate	Purposeful movement of limbs, head or neck produced
3	Poor	Horse moved into sternal position or stood

Table 5: Scorecard of quality of recovery

Quality of analgesia		
Score	Quality	Character
1	Excellent	Horse capable of standing in a first attempt
2	Good	Horse remained calm and needed two attempts to stand
3	Moderate	Horse remained calm but needed more than two attempts to stand
4	Poor	Excitement during recovery with danger of injury and needed more than one attempt to stand
5	Very poor	Severe excitement during recovery with injury

Results and Discussion

Sedation parameters

The time for sedation and quality of sedation were presented in Table 6. The mean time for sedation in minutes was 3.52 ± 0.55 and 2.74 ± 0.44 in group XKG and group DKG respectively. No significant difference of time of sedation and quality of sedation was observed between groups. However, in the present clinical study group, DKG showed a decrease in sedation times, which can be attributed to the combined effects of dexmedetomidine in combination with acepromazine and butorphanol, synergistically enhancing the sedative properties. Additionally, dexmedetomidine, as a potent alpha-2 agonist, significantly contributes to the overall sedative effect (Valverde 2010, Rezende *et al.* 2015) [25, 19]. In both groups, acepromazine produced better calming and anxiolytic effects, results the safe handling of animals for administering drugs. Acepromazine and butorphanol were together acted as neuroleptanalgesia synergistically with alpha-2 agonist producing profound to strong sedation without any deleterious effects. Similar findings have been reported by Pequito *et al.* (2013) [18] and Jishnu (2016) [10].

Table 6: Mean $\pm$ SE values of time for sedation and Median $\pm$ SD values of quality of sedation in group XKG and DKG.

Group	Time of sedation (min)	Quality of sedation score	Response to tactile score	Response to auditory stimulation score
XKG	3.52 ± 0.55	1.54 ± 0.54	2.00 ± 0	1.54 ± 0.54
DKG	2.74 ± 0.44	1.00 ± 0.4	2.00 ± 0.75	1.00 ± 0.51

* Significant $p < 0.05$

Induction parameters

The time of induction and quality of induction were presented in Table 7. The mean time for induction of anaesthesia was 91.66 ± 3.80 and 70.83 ± 4.36 seconds in groups XKG and DKG, respectively. The significant difference in the time of induction was observed between groups. No significant difference in the quality of induction was observed between groups. Similar findings have been reported by Jishnu (2016) [10], indicating a rapid and smooth

induction of anaesthesia after administering a combination of acepromazine and alpha-2 agonists as pre-anaesthetic, followed by intravenous administration of ketamine (2.2 mg/kg/b.wt). The onset of induction was influenced by the dosage of acepromazine and the specific alpha-2 agonist used, as reported by Marntell *et al.* (2006) [16] and Hall *et al.* (2014) [7].

Table 7: Mean $\pm$ SE values of time for induction and Median $\pm$ SD values of quality of induction in group XKG and DKG.

Group	Time for induction (sec)	Quality of induction score
XKG	$91.66 \pm 3.80^*$	2.00 ± 0.89
DKG	70.83 ± 4.36	1.00 ± 0.51

* Significant $p < 0.05$

Quality of anaesthesia

In both groups corneal, palpebral and rectal pinch reflexes were sluggish to absent until the completion of surgery. In both groups, muscle relaxation and analgesia were good to excellent during surgical anaesthesia. There was no significant difference in the quality of anaesthesia between both groups. Both groups produced adequate quality of anaesthesia during surgery.

Duration and maintenance of anaesthesia

In the present clinical study, the mean duration of maintenance anaesthesia using the triple drip method was found to be 66.66 ± 15.42 minutes in group I (XKG) and 45.83 ± 8.60 minutes in group II (DKG). These durations reflect the time during which the anaesthesia was maintained to keep the animals in a stable and controlled state throughout the surgical procedure. By utilizing CRI, the anaesthetic regimen can be finely adjusted, resulting in a stable and consistent level of anaesthesia throughout the surgery. The administered doses of drugs in the mixture were calculated and corrected to milligram/microgram per kilogram body weight per hour requirement in between groups. The duration and maintenance dose of anaesthesia were presented in Table 8. There was no significant difference between CRI doses between groups. During the entire surgical period, the continuous rate infusion (CRI) of the mixture proved to be highly effective in providing an excellent and balanced state of anaesthesia. Hopster *et al.* (2014) [8], Bettschart-Wolfensberger *et al.* (2005) [3] and Nanda *et al.* (2014) [17] conducted studies using various protocols involving the triple drip method with xylazine/dexmedetomidine, ketamine, and muscle relaxant in equines. These studies reported similar findings, indicating that the same dose of the triple drip combination was required to maintain effective surgical anaesthesia. This consistent result suggests that the combination of xylazine/dexmedetomidine, ketamine, and guaifenesin provided a reliable and stable state of anaesthesia throughout the surgical procedures in horses. In our study, the DKG group necessitated a mean dose of $6.07 \mu\text{g/kg/hr}$ of the dexmedetomidine combination in the triple drip for maintaining surgical anaesthesia. This dosage was observed to be lower than the previously recommended dose of $7 \mu\text{g/kg/hr}$ for sufficient maintenance during surgical procedures (Hopster *et al.* 2014) [8].

Table 8: Mean $\pm$ SE values of duration and maintenance dose of anaesthesia in group XKG and DKG.

Group	Duration of anaesthesia (min)	CRI dose (mL/kg/hr)	Triple drip	Dose of triple drip
XKG	66.66 $\pm$ 15.42	2.32 $\pm$ 0.44	Xylazine (mg/kg/hr)	1.16 $\pm$ 0.22
			Ketamine (mg/kg/hr)	4.65 $\pm$ 0.88
			Guaifenesin (mg/kg/hr)	116.43 $\pm$ 22.11
DKG	45.83 $\pm$ 8.60	2.42 $\pm$ 0.12	Dexmedetomidine (μ g/kg/hr)	6.07 $\pm$ 0.30
			Ketamine (mg/kg/hr)	4.8 $\pm$ 0.24
			Guaifenesin (mg/kg/hr)	121.45 $\pm$ 6.11

* Significant $p < 0.05$ **Recovery parameters**

Significant differences were observed for time to first head lift, sternal recumbency, standing time and quality of recovery between groups were presented in Table 9. The observed longer time for head lift up (righting reflex) in group XKG compared to group DKG can be attributed to the differences in the elimination of half-lives of the drugs. Xylazine has an average elimination half-life of 40 to 50 minutes, as reported by Villar *et al.* (1981) [26], while dexmedetomidine has a shorter elimination half-life of approximately 20 minutes, as reported by Bettschart-Wolfensberger *et al.* (2005) [3]. The majority of animals in a state of excitement-free sternal recumbency typically spent a minimum of 5 to 10 minutes before being able to stand. This period allows for a gradual and stable transition from lying down to an upright standing position. The faster elimination of dexmedetomidine likely contributed to a quicker recovery from the anaesthesia-induced state. Additionally, ketamine, known for its rapid tissue redistribution and hepatic metabolism, contributed to the swift elimination of the drug without the presence of benzodiazepines, as reported by Kaka *et al.* (1980) [12]. This combination of factors led to a

more efficient elimination of the drug. As a result, most animals in group II were able to stand up successfully on their first attempt without exhibiting any signs of excitement. This smooth recovery process allowed the animals to transition back to a normal state more quickly and effectively. Similar findings have been reported by Yamashita *et al.* (2000) [28] and Hopster *et al.* (2014) [8], who utilized dexmedetomidine as an alpha-2 agonist in their continuous rate infusion protocols. In group DKG showed better quality of recovery compared to group XKG, which can be attributed by many factors faster drug elimination, shorter duration of surgery, individual variations. Most of the animals in group DKG showed an excellent quality of recovery, with horses able to stand on their own in the first attempt without assistance, exhibiting mild ataxia. In group XKG showed very good quality of recovery horses able to stand on the first to second attempt with assistance and mild to moderate ataxia. These findings are consistent with previous studies conducted by Marcilla *et al.* (2012) [15] and Bettschart-Wolfensberger and Larenza (2007) [2], which also reported a better quality of recovery in animals.

Table 9: Mean $\pm$ SE values of recovery parameters and Median $\pm$ SD values of quality of recovery

Group	Time for first head lift (min)	Time for sternal recumbency (min)	Time for standing (min)	Quality of recovery
XKG	43.66 $\pm$ 9.59**	56.83 $\pm$ 12.57*	71.33 $\pm$ 14.30*	2.00 $\pm$ 0.75*
DKG	20.83 $\pm$ 2.21	27.33 $\pm$ 3.26	36.66 $\pm$ 3.84	1.00 $\pm$ 0.40

* Significant $p < 0.05$ ** Significant $p < 0.01$ **Clinicophysiological parameters**

In both groups, heart rate was significantly lower than preanaesthetic values after induction and maintained throughout surgical period were presented in the Table 10. The observed reduction in heart rate after induction can be attributed to the potent cardiovascular depression caused by the alpha-2 agonists used in both groups. Dexmedetomidine, in particular, may induce slightly more depression than xylazine, but this effect is of short duration and the heart rate quickly returns to the normal anaesthetic range and also its secondary compensatory effect of high vascular resistance produced peripheral vasoconstriction mediated by α_{2B} receptors in vascular endothelial tissues (Kable *et al.* 2000; Giovannitti *et al.* 2015) [11, 6]. Moreover, dexmedetomidine does not have direct effect on cardiac muscles. The decrease in respiration rate observed among the groups can be attributed to the suppressive effects on baroreceptors and adrenergic receptors caused by the administration of xylazine, dexmedetomidine and total intravenous anaesthesia (TIVA). These findings are consistent with the results reported by Hopster *et al.* (2014) [8], Sleiman *et al.* (2016) [21]. In both study groups, the rectal temperature exhibited a gradual but non-significant decrease

during the maintenance of anaesthesia, returning to baseline values after the recovery period. This decline in rectal temperature can be attributed to the comparatively lower rate of oxygen utilization and basal metabolic rate observed under anaesthesia compared to conscious horses. The reduction in basal metabolism is influenced by the effects of anaesthesia and adjunctive medications, which can interfere with thermoregulatory centers and muscular activity. Additionally, the depletion of catecholamines in the thermoregulatory centers caused by alpha-2 agonists can make horses susceptible to either hypothermia or hyperthermia depending on the environmental temperature (Lemke 1993) [14]. Following premedication and induction, both groups exhibited a significant decrease in the saturated partial pressure of oxygen, which can be attributed to the respiratory depression caused by the alpha-2 agonist. This decrease in oxygen saturation probably happened as is commonly seen in horses under general anaesthesia because of lateral recumbency is associated with the development of ventilation-perfusion mismatches and the shunting of blood through the lungs resulting in less than optimal oxygenation (Hubbell 1999) [9] (Thakur *et al.* 2011) [24].

Table 10: Mean $\pm$ SE values of physiological parameters in group XKG and DKG

Parameter	Group	Preanaesthesia	After induction	15 min	30 min	45 min	60 min	After recovery
HR (BPM)	XKG	51.00 $\pm$ 2.35 ^{aA}	37.17 $\pm$ 2.07 ^{aA}	36.33 $\pm$ 2.48 ^{aA}	37.83 $\pm$ 3.97 ^{aA}	36.80 $\pm$ 4.21 ^{aA}	37.00 $\pm$ 2.51 ^{aA}	48.00 $\pm$ 2.58 ^{bA}
	DKG	49.66 $\pm$ 1.81 ^{bA}	29.83 $\pm$ 2.82 ^{aB}	29.17 $\pm$ 2.56 ^{aA}	32.16 $\pm$ 2.28 ^{aA}	34.00 $\pm$ 5.03 ^{aA}	32.50 $\pm$ 6.50 ^{aA}	45.67 $\pm$ 0.95 ^{bA}
RR (breath/min)	XKG	20.16 $\pm$ 1.60 ^{bA}	8.00 $\pm$ 0.73 ^{aA}	7.66 $\pm$ 1.05 ^{aA}	8.33 $\pm$ 1.33 ^{aA}	7.40 $\pm$ 0.92 ^{aA}	8.00 $\pm$ 1.15 ^{bA}	17.16 $\pm$ 1.04 ^{bA}
	DKG	20.50 $\pm$ 2.39 ^{bA}	8.83 $\pm$ 0.54 ^{aA}	6.83 $\pm$ 0.54 ^{aA}	6.33 $\pm$ 0.55 ^{aA}	6.66 $\pm$ 0.33 ^{aA}	7.50 $\pm$ 1.50 ^{aA}	16.66 $\pm$ 0.80 ^{bA}
RT (°F)	XKG	100.7 $\pm$ 0.17 ^{aA}	100.48 $\pm$ 0.20 ^{aA}	100.10 $\pm$ 0.42 ^{aA}	100.38 $\pm$ 0.18 ^{aA}	100.30 $\pm$ 0.13 ^{aA}	99.87 $\pm$ 0.31 ^{aA}	100.03 $\pm$ 0.17 ^{aA}
	DKG	99.96 $\pm$ 0.20 ^{bB}	99.48 $\pm$ 0.31 ^{abB}	98.55 $\pm$ 0.40 ^{abB}	98.03 $\pm$ 0.49 ^{abB}	98.33 $\pm$ 1.18 ^{abA}	97.45 $\pm$ 1.45 ^{abA}	99.46 $\pm$ 0.09 ^{abA}
SpO ₂ (%)	XKG	97.16 $\pm$ 0.40 ^{bcA}	93.83 $\pm$ 1.77 ^{abA}	93.33 $\pm$ 1.25 ^{abA}	93.33 $\pm$ 1.08 ^{abA}	94.00 $\pm$ 1.04 ^{abA}	94.66 $\pm$ 0.33 ^{abcA}	98.00 $\pm$ 0.25 ^{bcA}
	DKG	98.33 $\pm$ 0.40 ^{dA}	94.33 $\pm$ 0.55 ^{bcA}	93.00 $\pm$ 1.03 ^{abA}	91.83 $\pm$ 0.65 ^{aA}	93.80 $\pm$ 0.73 ^{abcA}	95.33 $\pm$ 0.33 ^{cA}	98.00 $\pm$ 0.36 ^{dA}

Means bearing different small alphabet (a, b, c, d) superscript indicates significant difference ($p < 0.05$) value within group at different time intervals.

Means bearing different capital alphabet (A, B) superscript indicates significant difference ($p < 0.05$) value between the groups at corresponding time intervals.

Conclusions

In both groups, XKG and DKG the TIVA combination provided better maintenance of surgical anaesthesia in horses. The DKG group showed shorter and excellent quality of sedation and induction parameters than the XKG group. The dexmedetomidine group obtained half the time taken for recovery time compared to the XKG group, and also had a superior quality of recovery compared to the xylazine group. The DKG combination provided stable and predictable changes on cardiorespiratory parameters during anaesthesia compared to the XKG group. Overall, dexmedetomidine based TIVA showed better results than xylazine based TIVA combination. Thus, dexmedetomidine is a better alternative in many ways for achieving balanced anaesthesia in horses.

Authorship Contribution

Rajesh kumar K did research work and prepared the manuscript for submission, J V Vadalia guided for planning of work, A A vagh minor guide helped in data analysis, R H Bhatt member of research committee and helped in editing the manuscript and S H Zalavadiya and Sanjaykumar biradar helped in execution of research work.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

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