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ARAŞTIRMA/RESEARCH

Effect of intraoperative esmolol infusion on postoperative stress response in a group of laparoscopic cholecystectomy patients

Bir grup laparoskopik kolesistektomi hastasında intraoperatif esmolol infüzyonunun postoperatif stres yanıt üzerine etkisi

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Abstract

Purpose: We aimed to analyze effects of esmolol on intraoperative anesthetic-postoperative analgesic requirements, postroperative cortisol and prolactin levels.
Material and Methods: Sixty patients have been included. Study groups were as follows; 1: Esmolol infusion was added to propofol and remifentanil, 2: Only propofol and remifentanil, 3: Esmolol infusion was added to desflurane and remifentanil, 4: Only desflurane and remifentanil was used. Preoperative and postoperative cortisol and prolactin levels were measured.
Results: Analgesic requirements were significantly lower in group 1 and was lower in group 3 compared to group 4. Heart rates were significantly lower in esmolol groups (group 1 and 3) compared to their controls. Prolactin levels significantly increased postoperatively in all groups compared to preoperative levels. We observed a significant decrease in cortisol levels postoperatively in group 1 compared to preoperative levels.
Conclusion: Using adjuvant esmolol during anesthetic maintenance of laparoscopic cholecystectomy patients decreases anesthetic – analgesic requirements without causing any hemodynamic instability, and supresses postoperative cortisol response but does not have any significant effect on postoperative prolactin response.

Key words: Esmolol, postoperative stress response, cortisol, prolactin

Öz

Amaç: Çalışmada esmololün intraoperatif anestezik-postoperatif analjezik gereksinimi, postoperatif kortizol ve prolaktin düzeylerine etkisini araştırmayı amaçladık.
Gereç ve Yöntem: Çalışmaya 60 hasta dahil edilmiştir. Çalışma grupları şu şekilde dizayn edildi; 1: Esmolol infüzyonuna propofol ve remifentanil eklendi, 2: Sadece propofol ve remifentanil, 3: Esmolol infüzyonuna desfluran ve remifentanil eklendi, 4: Sadece desfluran ve remifentanil kullanıldı. Ameliyat öncesi ve sonrası kortizol ve prolaktin seviyeleri ölçüldü.
Bulgular: Analjezik gereksinimi tüm gruplar içinde grup 1'de anlamlı olarak düşüktü ve grup 4 ile karşılaştırıldığında grup 3'te düşük bulundu. Kalp hızı esmolol gruplarında (grup 1 ve 3) kontrol gruplarına göre anlamlı olarak daha düşüktü. Prolaktin düzeyleri bütün gruplarda preoperatif değerlere göre postoperatif dönemde anlamlı yüksek bulundu. Ameliyat öncesi seviyelere ile karşılaştırıldığında postoperatif kortizol düzeylerinde grup 1de anlamlı bir azalma gözlendi.
Sonuç: Laparoskopik kolesistektomi hastalarında anestezi yönetiminde adjuvan esmolol kullanımı herhangi bir hemodinamik instabiliteye neden olmadan anestezik - analjezik gereksinimini azaltıp postoperatif kortizol yanıtı baskılarken ameliyat sonrası prolaktin yanıtı üzerinde önemli bir etkisi yoktur.

Anahtar kelimeler: Esmolol, postoperatif stres yanıt, kortizol, prolaktin

INTRODUCTION

Laparoscopic cholecystectomy is a daily routine procedure with low cost and high patient satisfaction by developments in surgical and anesthetic techniques. Intra and postoperative hemodynamic stability and efficient analgesia is important to decrease incidence of postoperative complications[1,2] . In these patients hemodynamic stress responses like hypertension and tachycardia might develop as a reflex to endotracheal intubation or surgical intervention itself.

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Insufflation of CO_2 into peritoneal cavity might also trigger this response. Sympathoadrenergic reflex causes some metabolic and neuroendocrine reactions. Increased catecholamine secretion results in increased blood pressure and tachycardia. These might increase myocardial O_2 requirements but also decrease coronary blood flow and diastolic filling duration. This situation could be well tolerated in otherwise healthy patients however could have devestating results in elder patients with ischemic heart disease or comorbidities like diabetes mellitus.

Surgical stress response is characterized by increased serum levels of catecholamines, cortisol, antidiüretic hormone (ADH), growth hormone (GH), glucose, lactate and their metobolites. This increase is closely related with the severity of surgical intervention and is usually higher in abdominal surgeries. Plasma concentrations of stress hormones might also increase secondary to side effects of some anesthetic agents.

Different techniques or anesthetic agents could be used to decrease hemodynamic response and related postoperative complications[2-4]. Increasing volatile anesthetic concentrations and/or opioid usage are some methods that could be preferred[2].

Sympatholytic agents decrease hemodynamic response and so requirement for opioids. These agents are alternatives for opioids and also might decrease requirements for intravenous or inhalation anesthetics [2, 5]. In this study we aimed to analyze effects of esmolol, a cardioselective beta-1 (β_1) adrenergic receptor antagonist, on intraoperative anesthetic - postoperative analgesic requirements, postroperative cortisol and prolactin levels.

MATERIAL AND METHODS

Study was designed as a prospective study and was approved by local ethical committee (Ethical Committee of the Kecioren Traning and Research Hospital, Date: 09.01.2013/ Number: 174).

Sixty patients aged between 18-60 years who underwent laparoscopic cholecystectomy have been included. The patients were provided with details of the study to which they gave a written informed consent. Exclusion criterias were as follows; previously known cardiovascular disease, severe hemodynamical instability during operation [mean blood pressure (MBP) < 70 mmHg], chronic opioid usage, asthma, being obese or underweighted (body mass index > 30 or < 18.5), diabetes mellitus, using β blockers or calcium channel blockers.

No premedications were used before operation. Electrocardiographic (ECG), invasive intraarterial blood pressures, MBP, peripheral oxygen saturations (SpO_2) ve bispectral index (BIS) monitorizations were performed and recorded as study data.

Propofol 2.5 mg/kg, remifentanil 1μg/kg and vecuronium 0.1 mg/kg were used for induction in all patients. %50 O_2 and fresh air mixture was used during mechanical ventilation. End-tidal CO_2 ($ETCO_2$) levels were aimed to be between 35-45 mmHg and fresh gas flow rate was 3 lt/min in all patients.

Study groups were as follows;

Group 1: After induction, 5 minute esmolol infusion (total dose 1 mg/kg) was used. Peroperative esmolol dose was planned as 10 μg/kg/min. Maintenance anesthetics were 75-85 μg/kg/min propofol and 0.2 μg/kg/min remifentanil.

Group 2: Maintenance anesthetics were 75-85 μg/kg/min propofol and 0.2 μg/kg/min remifentanil. No esmolol infusion was used.

Group 3: After induction, 5 minute esmolol infusion (total dose 1 mg/kg) was used. Peroperative esmolol dose was planned as 10 μg/kg/min. Maintenance anesthetics were %4-8 desflurane and 0.2 μg/kg/min remifentanil.

Group 4: Maintenance anesthetics were %4-8 desflurane and 0.2 μ/kg/min remifentanil. No esmolol infusion was used.

Group 2 was designed as control for group 1 and group 4 was designed as control for group 3. Adjustments in esmolol and other anesthetic drug dosages were done according to MBP and heart rates of all individual patient as follows. Propofol and desflurane concentrations were changed continuously during operation by aiming BIS values between 40-60.

Intravenous atropine and ephedrine were planned to be used in case of any intraoperative bradycardia (40 pulse/min) or hypotension (MBP < 70 mmHg). In case of a decrease in heart rates and MBP near to above mentioned critical levels we first decreased remifentanil infusion rates and then decreased esmolol infusion rates. Total requirements of propofol, remifentanil, esmolol and desfluran were calculated and recorded for each patient.

All patients were followed up in postoperative critical care (PACU) unit for at least 30 minutes after surgery. Postoperative ECG, MBP, heart rates, peripheral SpO2 monitorizations were performed and recorded as study data. 10 mg metoclopramide iv was applied to all patients in PACU. All patients were discharged from PACU to standart care clinics after they had an Aldrete score < 9 and they have been followed up for another 24 hours for PNV and analgesic requirements.

Preoperative cortisol and prolactin levels were measured from a venous blood sample which was drawn just before initiation of anesthesia procedure and intubation. Postoperative cortisol and prolactin levels were measured from a venous blood sample which was drawn after 24 hours of leaving PACU. Cortisol and prolactin levels were studied with a Beckman Coulter, UniCel Dxl 800 Access Immunoassay System (CA, USA).

Statistical analysis

Statistical Package for Social Sciences (SPSS for Windows, Chicago, IL, USA) version of 14.0 was used for data analysis. Data were submitted to a frequency distribution analysis by Kolmogorov-Smirnov's test. Values displaying normal distribution were expressed as the mean ± SD and values with skew distribution were expressed as median (interquartile range).

Differences between numeric variables were tested with One-Way ANOVA or Kruskal-Wallis tests where appropriate. Tukey test was used for post-hoc analyses. Paired samples t-test or Wilcoxon signed-rank test was used to compare two related samples. Categorical data were compared by chi-square or Fisher's tests. The value of confidence interval was accepted as 95% and statistical significance was accepted as: "p<0.05".

RESULTS

Sixty laparoscopic cholecystectomy patients (45 female, age; 47.8 ± 12.1 years) were included. Study groups were statistically similar in means of demographic (age and gender distribution) chatracteristics (Table 1). Surgery and anesthesia durations were also similar however there was a tendency for increased surgery (p: 0.054) and anesthesia durations (p: 0.097) in group 1 and group 2 compered to groups 3 and 4 (Table 1). These durations were similar when esmolol groups were compared with only their controls (group 1 vs 2 and group 3 vs 4).

Mean BIS values were similar between groups and were between 40-60 (p: 0.270). When compared in means of hemodynamical parameters heart rates were significantly lower in esmolol groups (group 1 and 3) compared to their controls (p: 0.001) however MBP values were similar in all groups (p: 0.594). Heart rates and MBP values in PACU were similar between groups (p: 0.327, 0.094 respectively). Comparison of esmolol groups with controls in means of anesthetic requirements revealed that there is a significant decrease in desflurane, propofol and remifentanil requirements (p: 0.024, 0.03, 0.026 respectively).

In means of preoperative prolactin and cortisol levels study groups were similar. Prolactin levels significantly increased postoperatively in all groups compared to preoperative levels (p: 0.005 – 0.001, Table-1 and Figure-1). However there was no significant difference between study groups in means of postoperative prolactin levels when compared to each other (p: 0.478).

We also observed a significant decrease in cortisol levels postoperatively in group 1 compared to preoperative levels (p: 0.037, Table-1, Figure_2). There was also a decrease in postoperative cortisol levels in group 3 but it did not have statistical significancy (p: 0.1). In groups 2 and 4 there was a significant increase in postoperative cortisol levels compared to initial values (p: 0.003, 0.008 respectively). When we compared postoperative cortisol values of study groups with each other we observed that control groups (groups 2 and 4) had significantly higher cortisol levels compared to groups 1 and 3 (p: 0.034, Table-1, Figure-2).

DISCUSSION

Anesthesia induction, laryngoscopy and tracheal intubation might induce a stress response that increase incidence of some intraoperative or postoperative complications like hemodynamic instability, myocardial ischemia and infarction [6]. Epipharyngeal and laryngopharyngeal irritation induces cervical sympathetic system activation and catecholamine secretion [7]. Increased serum catecholamine levels cause some hemodynamic changes like hypertension and tachycardia [8]. These hemodynamic changes not only increase myocardial O_2 requirements but also increase intracranial and intraocular pressures and might cause specific risks in susceptible patients[9].

In laparascopic surgeries pneumoperitonium is an additional risk factor. Insufflation of CO_2 causes a rapid increase in arterial and central venous blood pressures, heart rates and systolic vascular resistance [10,11]. These factors also contribute to increased myocardial O_2 requirements and trigger cardiovascular complications in patients with decreased cardiac reserve[12]. Vasopressor response is a result of combined activation of sympathetic, hypothalamic and renin angiotensin aldosteron systems. Functional magnetic resonance imaging studies reported that there is a hippocampal activation during emotional distress, fear or anxiety. This hippocampal activation is thought to be secondary to a stress related factor like norepinephrine that increases hippocampal neuronal activity. N-metil D-aspartat (NMDA) and adrenergic receptors at hippocampus also play role in nociception. Blocking these receptors decrease amplitude of patients' perception of pain[13].

Table-1. Comparison of study groups

	Group 1 (n:12)	Goup 2 (n: 15)	Group 3 (n: 21)	Group 4 (n: 12)	P value
Gender (F/M)	9/3	12/3	15/6	8/4	0.724
Gender (years)	44.3 ± 13.2	45.3 ± 14.2	51.7 ± 9.3	48,8 ± 11.9	0.318
Surgery duration (min)	79.1 ± 23.9	82.6 ± 31.3	62.2 ± 24.1	55.5 ± 23.5	0.054
Anesthesia duration (min)	92.1 ± 25.6	91.1 ± 35.7	77.7 ± 22.9	68.1 ± 24.8	0.097
Preoperative prolactin levels	8.9 (6.3)	7.7 (8.6)	6.2 (6.8)	9.6 (4.7)	0.484
Preoperative cortisol levels	14.8 (14.4)	11.4 (10.5)	13.1 (12.8)	13.1 (6.2)	0.79
Postoperative prolactin levels (ng/mL)	96.6 (38.4)	119.1 (112.5)	83.6 (101.6)	76.1 (91.4)	0.478, 0.005*, 0.001**
Postoperative cortisol levels (ng/mL)	10.8 (8.2)	15.3 (20.6)	10.3 (6.2)	18.8 (12.2)	0.034, 0.037***, 0.003†, 0.008‡
Intraoperative heart rate (pulse/min)	66.4 ± 9.1	77.4 ± 7.5	69.3 ± 6.4	72.8 ± 6.1	0.001
Intraoperative mean blood pressure (mmHg)	91 ± 15.7	92.1 ± 11.7	91.6± 8.3	86.6 ± 10.8	0.594
Heart rate in PACU (pulse/min)	63.6 ± 11.9	72.9 ± 12.4	67.4 ± 12.1	65.7 ± 15.6	0.327
Mean blood pressure in PACU (mmHg)	79.7 ± 15.1	89.1 ± 16.3	80.9 ± 13	76.8 ± 9.5	0.094
Mean BIS value	51.9 ± 20.2	51.7 ± 12.6	46.7 ± 9.4	43.4 ± 8.5	0.270
Propofol requirements (mL)	328.4 ± 173.8	530.1 ± 244.1	-	-	0.024*
Desflurane requirements (mL)	-	-	31.2 ± 12.3	43.6 ± 18.9	0.03**
Remifentanil requirements (mL)	174.6 ± 100.8	269.2 ± 105.2	132.9 ± 146.0	562.4 ± 152.4	0.026* 0.0001**

*, p level for pre-postoperative prolactin level comparisons for groups 1 and 4; **, p level for pre-postoperative prolactin level comparisons for groups 2 and 3; ***, p level for pre-postoperative cortisol level comparisons for group 1; †, p level for pre-postoperative cortisol level comparisons for group 3; ‡, p level for pre-postoperative cortisol level comparisons for group 4

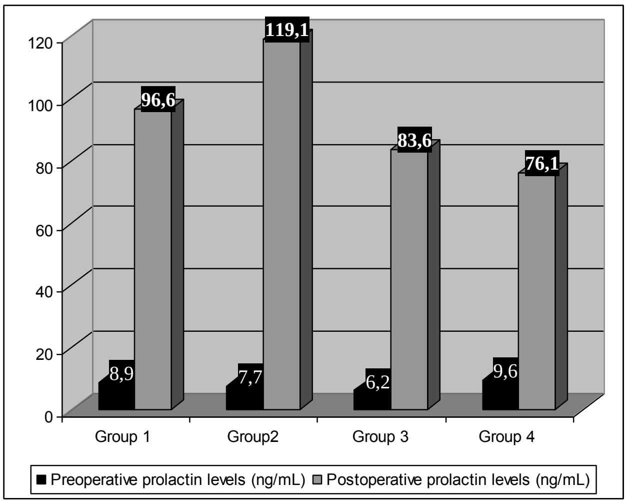

Figure 1. Comparison of pre and postoperative prolactin levels.

Prolactin levels significantly increased postoperatively in all groups compatred to preoperative levels (groups 1 and 4; p: 0.005, groups 2 and 3; p: 0.001). However there was no significant difference between study groups in means of postoperative prolactin levels when compared to each other (p: 0.478).

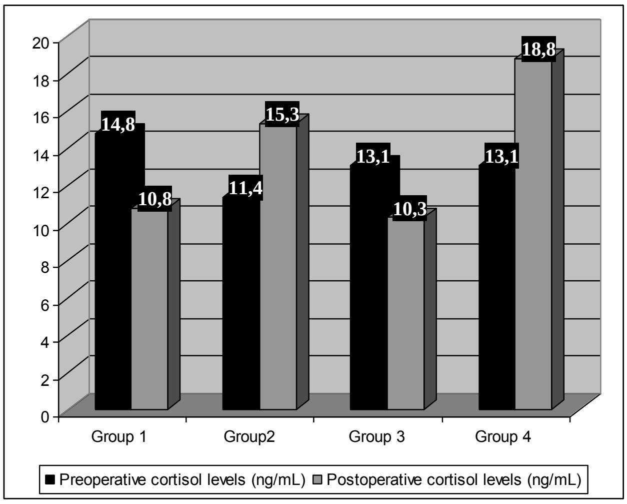

Figure 2. Comparison of pre and postoperative cortisol levels.

There was a significant decrease in cortisol levels postoperatively in group 1 compared to preoperative levels (p: 0.037). Decrease in in group 3 did not have statistical significancy (p: 0.1). In groups 2 and 4 there was a significant increase in postoperative cortisol levels compared to initial values (p: 0.003, 0.008 respectively). Postoperative cortisol values of control groups (groups 2 and 4) had significantly higher cortisol levels compared to groups 1 and 3 (p: 0.034).

Stress response to surgical interventions is characterized by increased plasma levels of catecholamines, cortisol, prolactin, ADH, GH, glucose, lactate, pyruvate and some other hormones and their metabolites. Increased levels of these hormones and other related molecules are related with the severity of surgical intervention.

Intraabdominal surgeries usually cause more severe stress responses compared to superficial surgeries.

Intravenous or inhalation anesthetics might also increase plasma levels of these stress hormones. This increase is an undesired side effect as this situation might cause not only hemodynamic instability but also intraoperative and postoperative catabolism.

Some modifications in anesthesia protocols are being researched by clinicians to decrease incidence of these complications[14-19]. In this study we examined a group of laparoscopic cholecystectomy patients for effects of adding esmolol in anesthesia protocol on serum prolactin and cortisol levels. We observed that in patients who received esmolol, serum cortisol levels significantly decreased postoperatively possibly indicating a decreased sympathetic activity. However there was a significant increase postoperative prolactin levels without any statistical difference between study groups.

When we compared study groups in means of hemodynamic parameters we also observed that intraoperative heart rates were significantly lower in esmolol groups (group 1 and 3) compared to their controls.Comparison of esmolol groups with controls in means of anesthetic - analgesic requirements revealed that there is a significant decrease in desfluran, propofol and remifentanil requirements.

Effects of β blockers in angina pectoris, hypertension and arythmia are very well known[20-22]. Using propranolol to decrease intraoperative myocardial ischemia in high risk patients is a common practice for anesthesiologists. However long half life of propranalol limits its' usage. Esmolol is an ideal β blocker that has shorter half life and higher cardioselectivity. Its' effect start fast and also gets eliminated in a short time with a half life of 9.2 ± 2 minutes[23]. It shows its' maximal effect on heart rate and blood pressure in 1-2 minutes after intravenous injection[24]. Esmolol could be used by intravenous infusion or boluses due to its' pharmacodynamic and pharmacokinetic properties

Esmolol supresses adrenergic response against laryngoscopy, tracheal intubation-extubation and peritoneal irritation due to CO_2 insuflation during laparoscopy[14]. Using esmolol infusion intraoperatively gives opportunity to control sympathetic system response and there by decrease myocardial O_2 consumption[25,26]. Depending on our findings we think that by close hemodynamic follow-up and titrating esmolol doses, anesthesiologist could avoid unwanted side effects of esmolol like hypotension, and also could use this dose titration advantage and decreased intraoperative heart rates to decrease myocardial O_2 requirements. Supporting our findings Smith and colleagues compared esmolol and alfentanil in means of hemodynamic stability in a group of arthroscopic surgery patients and reported that esmolol is a good alternative with less side effects [1].

We observed that addition of esmolol decreases remifentanil requirements significantly. In some studies remifentanil was reported to cause hypotension. Hogue and colleagues reported that 20% of patients who received remifentanil developed hypotension[27]. Schuttler and colleagues and McAtamney and colleagues also reported similar results in two different studies[28,29]. Depending on these findings we believe that adding esmolol in anesthesia protocols with remifentanil will significantly decrease hemodynamic complications and hypotension. According to our findings addition of esmolol also decreases requirements for propofol and desflurane. It could easily be foreseen that decreased anesthetic requirements will cause less side effects and also a decrease in economical cost. Supporting our findings Johansen and colleagues reported similar results. They compared effect of esmolol addition on propofol and 60% N_2O requirements and observed that esmolol significantly decreases requirements for both agents [5]. In two different studies Topçu and colleagues and Wilson and colleagues reported esmolol decreased both propofol and remifentanil requirements [30,31].

Main purpose of our study was to compare pre and postoperative levels of cortisol and prolactin in a group of patients who received or did not receive esmolol as a part of anesthesia protocol. We observed that prolactin levels significantly increased postoperatively in all groups compared to preoperative levels. We also observed a significant decrease in cortisol levels postoperatively in group 1 compared to preoperative levels. In groups 2 and 4 there was a significant increase in postoperative cortisol levels compared to initial values (Table 1). Effects of opioid agents on stress hormone response differs. Underlying mechanism of inhibition of stress response by high dose opioids is still not clear. Exogen narcotic analgesics play regulatory roles in synthesis of many hipophyseal hormones. Fentanil and new generation opioids decrease stress response more efficiently compared to morphine. Fentanil decreases hyperglisemic reaction and also decreases cortisol and growth hormone levels. Fentanil has a similar effect with morphine in means of increasing plasma catecholamine levels but contradictorily decreases plasma anti diuretic hormone and renin. New generation opioids like sufentanil, alfentanil and remifentanil were reported to be more efficient in means of these findings[32].

However in our study we observed an increase in cortisol levels in groups 2 and 4 who received higher doses of remifentanil compared to esmolol receiving patients. On the other hand in those patients who received esmolol we observed a significant postoperative decrease in cortisol levels. Depending on these findings we believe that esmolol is not only more efficient in means of decreasing stress response but also might decrease anesthesia cost by decreasing anesthetic requirements.

Since 1950's both ACTH and prolactin have been known to be secreted from hypohyseal gland as a stress response. Opioid receptors are thought to play role in secretion of prolactin. Endogen opioids like morphine, Met-enkephalin and β endophine all cause an increase in prolactin secretion, on the other hand naloxane was reported to decrease secretion[33].

Nearly all studies in this subject was about evaluation of hormonal stress response but a few of them evaluated both hormonal response and hemodynamic parameters. Evaluation of adrenalin and noradrenalin levels after sympathetic induction by laryngeal intubation is also the most commonly used method in these studies[34]. Previous studies reported that high or even medium doses of opioid analgesics like fentanyl are highly efficient in supressing catecholamine discharge[35]. Sahin and colleagues who evaluated hemodynamic responses against fentanyl and remifentanil reported a significant increase in prolactin levels of patients who received fentanyl[36]. Song et al also compared fentanyl and remifentanil and reported that remifentanil was more efficient in supressing endocrine stress response compared to fentanyl[37]. Despite of these findings remifentanil was also reported in several other studies to increase stress hormone levels in similar way to endogen opioids like morphine(***). In our study despite of lower doses of remifentanil in groups 1 and 3 we observed a similar incrase in postoperative prolactin levels in all study groups. Depending on these findings we think that decreasing remifentanil dose by co administration of esmolol does not have a significant effect on decreasing postoperative prolactin response.

As a conclusion we observed that using adjuvant esmolol during anesthetic maintenance of laparoscopic cholecystectomy patients decreases anesthetic – analgesic requirements without causing any hemodynamic instability, and supresses postoperative cortisol response but does not have any significant effect on postoperative prolactin response.

Preliminary data for this study were presented as a poster presentation at 48th Annual meeting of Turkish Society of Anesthesiology and Reanimation, 25-29 October 2014, Ankara, Turkey

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