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Toho Journal of Medicine Vol. 7 No. 1 掲載論文の紹介

Advances in the Treatment of Rheumatoid Arthritis

Tanaka E, Muraoka S, Nanki T

Toho J Med 7 (1): 1–10, 2021

要約 :

Rheumatoid arthritis (RA) is characterized by synovitis, bone erosion, and cartilage destruction, which ultimately lead to joint destruction. The pyramidal plan, which aims to attenuate symptoms, was the standard treatment for RA. However, advances in therapeutic agents mean that the maintenance of remission is now a realistic treatment goal. Recent treatments, including methotrexate, biological disease-modifying anti-rheumatic drugs, and Janus kinase inhibitors, achieve low disease activity and improve the prognosis of RA; however, not all patients exhibit favorable responses. Furthermore, the economic burden and adverse effects associated with these treatments have not yet been resolved. Therefore, the development of more effective and safer therapies is required. Advances in the treatment of RA have been discussed herein.

KEYWORDS: biologics, Janus kinase inhibitors, methotrexate, rheumatoid arthritis

Comparison of the Effect of Proton Pump Inhibitors on Capecitabine and S-1 in Gastric Cancer Treatment with Trastuzumab; A Multi-Institutional Analysis

Kikuchi Y, Yamashita H, Fujisaki M, Yoshimoto Y, Otsuka K, Nagaoka S, Fujita S, Tokuyama J, Satodate H, Isobe Y, Urakami H, Mitsumori N, Seto Y, Futawatari N, Yajima S, Oshima Y, Murakami M, Igarashi Y, Shimada H

Toho J Med 7 (1): 11–19, 2021

要約 :

Introduction: The effect of proton pump inhibitors on capecitabine- and S-1-based treatment for human epidermal growth factor receptor 2 (HER2)-positive gastric cancer is unknown. Therefore, we compared the effect of proton pump inhibitors between capecitabine- and S-1-based treatments for HER2-positive gastric cancer.

Methods: In a multi-institutional study, we retrospectively analyzed the effect of proton pump inhibitors on 155 HER2-positive advanced or recurrent gastric cancer patients who were treated with oral 5-fluorouracil (capecitabine or S-1) and trastuzumab. Capecitabine- and S-1-based treatments were compared in terms of the response rate and time to treatment failure, and the negative effects of proton pump inhibitors on the treatment response were evaluated. In this study, the primary endpoint was the response rate, and the secondary endpoint was time to treatment failure.

Results: There was no significant difference in the response rate between the capecitabine- and S-1-based treatments. However, in cases without proton pump inhibitor intake, the response rate significantly improved with capecitabine-based treatment rather than with S-1-based treatment ($P = 0.046$). Compared with the S-1-based treatment, the capecitabine-based treatment significantly prolonged the time to treatment failure ($P = 0.044$), including for patients with differentiated adenocarcinoma ($P = 0.035$).

Conclusions: For HER2-positive and differentiated gastric cancer, capecitabine-based treatment may be better than S-1-based treatment. Proton pump inhibitors might decrease capecitabine's effects and should be avoided to increase the response rate to capecitabine-based treatment.

KEYWORDS: proton pump inhibitor, HER2-positive gastric cancer, capecitabine, S-1, trastuzumab

Postoperative Acute Kidney Injury Associated with Anesthesia Induction in Extremely Hypertensive Patients Undergoing Elective Non-Cardiac Surgery

Morozumi K, Satomoto M, Hanai Y, Ochiai R, Kotake Y

Toho J Med 7 (1): 20–28, 2021

要約 :

Introduction: Some patients exhibit extreme hypertension before anesthetic induction. Although it is important to avoid hypotension during anesthesia to prevent major postoperative complications, it remains unknown how anesthetic hypotension should be managed in patients with hypertension. Therefore, we investigated the incidence of postoperative complications and their associations with low blood pressure during surgery in patients with a systolic blood pressure >200 mmHg before anesthetic induction.

Methods: We assessed the incidence of postoperative acute kidney injury (AKI), myocardial infarction (MI), and ischemic stroke. For postoperative AKI, we investigated the duration, between intubation and surgery initiation, for which the patients' mean arterial pressure (MAP) was below the threshold, and the duration from surgery initiation to the end of anesthesia. Based on these analyses, factors considered to be clinically associated with postoperative AKI were extracted and subjected to multivariate logistic regression analysis.

Results: In total, 274 patients were enrolled. Of these, 35 developed AKI and one experienced MI and ischemic stroke. The durations for which the MAP was <65, 70, and 75 mmHg between intubation and incision were significantly longer in the AKI group than in the non-AKI group ($P < 0.01$). Multivariate regression analysis revealed a statistically significant association between the duration of having a MAP <75 mmHg and postoperative AKI (adjusted odds ratio = 1.04, confidence interval=1.02-1.07, $P < 0.001$).

Conclusions: In patients with extreme hypertension before anesthetic induction undergoing elective non-cardiac surgery, a MAP <75 mmHg between intubation and incision may be an independent risk factor for postoperative AKI.

KEYWORDS: preinduction hypertension, anesthesia, surgery, postoperative complications, acute kidney injury

Comparison of First- and Second-Generation Drug-Eluting Stents for Bifurcation Stenting

Fujii T, Watanabe I, Nakanishi R, Amano H, Toda M, Ikeda T

Toho J Med 7 (1): 29–38, 2021

要約 :

Introduction: Percutaneous coronary intervention (PCI) for bifurcated lesions is challenging. We assessed the procedural performance and clinical outcomes of first- and second-generation drug-eluting stents (DES) in bifurcation stenting followed by the final kissing-balloon (FKB) technique.

Methods: We retrospectively analyzed 192 patients (222 lesions) who underwent PCI for bifurcated lesions. In all cases, lesions underwent stenting, followed by FKB. Clinical outcomes were compared for the two generations—first-generation (80 patients/88 lesions) vs. second-generation (112 patients/134 lesions). The primary endpoint was target-lesion failure (TLF), defined as cardiac death, target-lesion revascularization or target-lesion-related stent thrombosis at 2 years.

Results: TLF incidence was higher for first-generation DES than for second-generation DES (15.0% vs. 2.7%; $P < 0.01$). The first-generation DES (hazard ratio [HR]: 6.41, 95% confidence interval [CI]: 1.75-23.5, $P < 0.01$) and SYNTAX score (HR: 1.07, 95% CI: 1.01-1.13, $P = 0.02$) were predictors of TLF after bifurcation stenting followed by FKB. PCI for the left main trunk (HR: 6.22, 95% CI: 1.55-25.0, $P = 0.01$) and SYNTAX score (HR: 1.09, 95% CI: 1.02-1.17, $P = 0.02$) were found to be associated with increased TLF for patients who were treated with first-generation DES, but no prognostic factor of TLF was found for patients with second-generation DES.

Conclusions: In bifurcation stenting followed by FKB, outcomes are better for second-generation DES than for first-

generation DES.

KEYWORDS: percutaneous coronary intervention, drug-eluting stent, bifurcation stenting, final kissing-balloon technique, target-lesion revascularization

Comparison of Cardiac Output and Stroke Volume Calculated by Pulse Wave Transit Time at the Fingertip Versus at the Toe

Hasegawa M, Ochiai R, Kotake Y

Toho J Med 7 (1): 39—47, 2021

要約 :

Introduction: The estimated continuous cardiac output (esCCO), which is a noninvasive way of measuring cardiac output, enables the measurement of vital parameters to evaluate the oxygen supply/demand balance of organs and tissues. The esCCO is optimized for measurement using a fingertip pulse oximeter; however, in some instances, various conditions prevent attaching a probe to the fingertip. Thus, the cardiac index (esCI) and stroke volume index (esSVI) at the fingertip and toe were simultaneously measured and examined to determine whether the values measured at the toe could be used as an alternative to estimate those parameters and predict fluid responsiveness.

Methods: In total, 31 otorhinolaryngology surgery cases under general anesthesia were examined. We statistically analyzed the compatibility and trending ability of the SVI and CI values between at the fingertip and toe. Further, we were able to examine fluid responsiveness during hypotension. These data were then used to create a receiver operating characteristic curve and determined cutoffs of stroke volume variation (SVV) at the toe in order to predict greater than 10% increase in esSVI at the fingertip.

Results: As per our findings, esSVI and esCCI measured at the fingertip and toe exhibited significantly high compatibility and trending ability. Further, the cutoff value for greater than 10% increase in esSVI at the fingertip was toe SVV of 7.0%.

Conclusions: esSVI and esCI measured at the toe have exhibited high compatibility and trending ability with the data obtained at the fingertip; concurrently, they enabled the evaluation of fluid responsiveness. We confirmed that even when physical limitations prevent the attachment of a pulse oximeter probe to the fingertip, the SVI and CI can be well estimated at the toe.

KEYWORDS: estimated continuous cardiac output (esCCO), cardiac output, cardiac index, stroke volume index, stroke volume variation

LR11, an LDL Receptor Gene Superfamily Member, Represses the Norepinephrine-Induced Expression of Uncoupling Protein 1 in Primary Cultured Beige Adipocytes

Nakamura S, Jiang M, Oka R, Yamaguchi T, Hiruta N, Ebinuma H, Schneider W J, Tatsuno I, Bujo H

Toho J Med 7 (1): 48—56, 2021

要約 :

Introduction: The soluble form of LR11 (sLR11) inhibits thermogenesis via BMPs/TGF β signaling pathways in adipocytes. Mice lacking LR11 are protected from diet-induced obesity associated with increased browning of subcutaneous white adipose tissue (WAT) and hypermetabolism. However, the mechanism underlying the recruitment of beige adipocytes has not been elucidated. In this paper, we have investigated the expression of LR11 in the differentiation and norepinephrine-induced activation of cultured beige adipocytes.

Methods: LR11 mRNA levels were analyzed in cultured beige adipocytes differentiated from human immortalized adipose-derived stromal cells or from the subcutaneous WAT of wild-type (WT) and *Lr11*^{-/-} mice. The concentrations of sLR11 were measured by an ELISA specific for murine sLR11.

Results: In the course of browning adipogenesis of human stromal cells, LR11 mRNA levels decreased at the begin-

ning and subsequently increased together with uncoupling protein (UCP) 1, β 3-adrenergic receptor, lipoprotein lipase, and adiponectin. The LR11 transcript levels in the differentiated cells were transiently decreased by incubation with norepinephrine, and this change was in clear contrast to the increase of UCP1 mRNA levels. The mRNA levels of UCP1 in murine *Lr11^{-/-}* beige adipocytes were significantly increased compared with those in WT beige adipocytes, regardless of norepinephrine stimulation. Finally, the amounts of sLR11 released from murine WT beige adipocytes were decreased by incubation with norepinephrine.

Conclusions: LR11 potentially represses the norepinephrine-induced expression of UCP1 in differentiated beige adipocytes. The sLR11-mediated repression of the key molecule in thermogenesis may be involved in the sympathetic activation of the recruitment of beige adipocytes in subcutaneous fat.

KEYWORDS: LR11, adipogenesis, thermogenesis, UCP1, beige

Change of Plasma Ketone Bodies and Skin Gas Acetone in Hemodialysis Patients

Suzuki T, Sasaki Y, Komatsu F, Maeda T, Suzuki K, Urita Y

Toho J Med 7 (1): 57—65, 2021

要約 :

Introduction: Ketone body metabolism increases under various pathological conditions, including insulin resistance, inflammation, and heart failure, which are common in hemodialysis patients. This study investigated whether plasma ketone bodies and skin-gas acetone are useful biomarkers of metabolic conditions during hemodialysis.

Methods: Twenty patients with end-stage renal disease undergoing maintenance dialysis for at least 9 months were enrolled. To measure plasma ketone body concentrations before and immediately after hemodialysis, blood samples were collected from the shunt vessel. Also, we measured acetone concentration in the vapors emanating from the skin.

Results: Plasma ketone body concentrations increased 6-fold after hemodialysis, with a remarkable increase of β -hydroxybutyrate (BOHB) and plasma BOHB/acetoacetate ratio. Conversely, no significant change of skin-gas acetone concentration was observed. Therefore, no association was found between the concentration of plasma ketone bodies and skin-gas acetone. Increased ratio of glucose level and ketone bodies exhibited a positive correlation; however, other laboratory data did not. Increased ratio of plasma BOHB significantly correlated with water removal ratio.

Conclusions: We found a significant increase in BOHB-dominant plasma ketone bodies, which significantly correlated with the water removal ratio, and dissociation between the changes in skin-gas acetone and plasma ketone body concentrations after hemodialysis. These results suggest an association between two independently reported cardiovascular risk factors, plasma BOHB concentration and fluid removal amount in hemodialysis patients. Although no association between skin-gas acetone and plasma ketone bodies was observed, the dissociation suggests an increase in ketone body synthesis during hemodialysis.

KEYWORDS: acetone, plasma ketone body concentration, hemodialysis, end-stage renal disease, skin gas

Pain Intensity Measurement after Gynecological Laparoscopic Surgery Using the “Pain Vision™” System for the Quantitative Analysis of Perception and Pain Sensation

Katakura M, Nakaoka K, Taniguchi T, Maemura T, Morita M

Toho J Med 7 (1): 66—72, 2021

要約 :

Introduction: Postoperative analgesia is easier if the degree of pain and factors enhancing pain with each operation can be predicted more accurately. To assess postoperative pain after gynecological laparoscopic surgery, we evaluated the extent of pain before and after treatment using the visual analogue scale (VAS) and “Pain Vision™” system, which is a quantitative analyzer of sensory perception and pain.

Methods: In total, 33 cases of laparoscopic uterine myoma enucleation (LM group) and 41 cases of laparoscopic total hysterectomy (TLH group) were assessed using the VAS and “Pain Vision™” system. The changes in the pain degree, measured using “Pain Vision™”, were evaluated over time and examined. Briefly, to measure the pain degree, an electrode is attached to the forearm, the stimulus is applied, and the current perceptual threshold and the current value of pain are registered. These values are then applied to the following equation: degree of pain = (pain response current - minimum sensing current)/minimum sensing current.

Results: The standardized regression coefficients were 0.144 for VAS and 0.229 for Pain Degree. Importantly, these values were significantly different. This analysis suggests that LM is a factor that affects the values of VAS and Pain Degree rather than TLH.

Conclusions: The postoperative pain was stronger in the LM group than in the TLH group. Based on these results, postoperative pain management should be considered separately for each surgical procedure.

KEYWORDS: Pain Vision, post operative pain, laparoscopic surgery

Anesthetic Management and Postoperative Course of a Patient with Anti-N-Methyl-D-Aspartate Receptor Encephalitis Associated with Ovarian Teratoma

Kimura R, Koda K, Kimura H, Uzawa M, Sato K, Aiba Y, Ishida H, Kitamura T

Toho J Med 7 (1): 73–77, 2021

要約 :

A 32-year-old woman complained of fever, hallucinations, and seizures. Based on her symptoms and the presence of an ovarian tumor, anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis was suspected. Without waiting for specific antibody test results, she underwent emergency laparoscopic salpingo-oophorectomy. The patient received general anesthesia, which was maintained with midazolam, propofol, opioids, and rocuronium. Her anesthesia recovery was uneventful, and she had tracheal extubation after surgery. Postoperatively, her symptoms deteriorated, despite first-line immunotherapy using immunoglobulin, steroids, and plasmapheresis. She required respiratory support for central hypoventilation. As second-line immunotherapy, rituximab and cyclophosphamide were administered, resulting in gradual symptom improvement. Approximately five months after onset, she was discharged in an ambulatory condition. Early tumor resection, combined with immunotherapy, is recommended for anti-NMDAR encephalitis secondary to tumors. Since there are individual differences in the clinical courses of patients with this disease, careful perioperative management is essential.

KEYWORDS: anti-N-methyl-D-aspartate receptor encephalitis, laparoscopic salpingo-oophorectomy, anesthetic management, postoperative course

Radical Esophagectomy Combined with Resection of the Invaded Descending Aorta for T4 Barrett's Esophageal Carcinoma: A Case Report

Yajima S, Suzuki T, Okuma S, Fujii T, Nanami T, Oshima Y, Shiratori F, Funahashi K, Watanabe Y, Shimada H

Toho J Med 7 (1): 78–83, 2021

要約 :

A 58-year-old Japanese man was diagnosed with T4b (descending aorta) N2M1, stage IVB lower thoracic Barrett's esophageal adenocarcinoma. He was initially treated with definitive chemotherapy with cisplatin and 5-fluorouracil (FP therapy). After one course of FP therapy, he developed renal dysfunction complications. Computed tomography showed no remarkable change in the main tumor and metastatic lesion. Therefore, radical esophagectomy with resection of the invaded descending aorta and removal of the solitary metastatic lesion was performed. Superior mediastinal

dissection, esophageal transection, and left adrenal gland removal were performed simultaneously. The patient underwent curative resection but died of multiple hematogenous metastases 116 days postoperatively. As aortic infiltrates were infected, artificial blood vessel replacement was selected. Although he underwent radical esophagectomy, hematogenous metastases have occurred in the early postoperative period.

KEYWORDS: Barrett's esophageal adenocarcinoma, T4 aorta
