Comparison of Immunological Effect of Propofol and Thiopentone on the Immune System

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This study was designed to compare the immunological effect of thiopentone with propofol. By using TIVA technique first group patients were infused with propofol and second group infused with thiopentone. Many immunological and haematological tests were studied on samples obtained 30 min. before, 30 min. and 24 hr after the operation. The PPD test was also implemented before and after two days of anaesthesia. In the study at postoperative 30th min. decrease of IgG, IgM, IgA and C3 in the group used propofol and decrease of IgM, IgA and C4 in the group used thiopentone were significant ($p<0.05$). At postoperative 24th hours increases of the IgG, IgM, and C3 levels and decrease of IgA level in the first group and decrease of the IgA level in second group were significant ($p<0.05$). When compared the difference between the groups, difference of the decrease in the IgA level was significant ($p<0.05$). In the both groups, decreases of CD4, leucocyte and lymphocyte were significant ($p<0.05$). At postoperative 24th hours while CD4 and CD8 levels and lymphocyte counts were significantly increasing in the first group, just lymphocyte count increase was significant in the second group ($p<0.05$). When compared the difference between the groups, decreases of the leucocyte and lymphocyte counts in the first group were significant ($p<0.05$). The postoperative second days PPD results were significantly decreased in both group ($p<0.05$). We concluded that both agents especially propofol have an immunosuppressive effect. [Journal of Turgut Özal Medical Center 1997;4(2):187-192]

Key Words: *Immune system, propofol, thiopentone*

Propofol'un immun sisteme etkisinin tiyopental ile karşılaştırılması

Çalışmamızda, propofol ve tiyopental'in immünolojik etkilerinin karşılaştırılması amaçlanmıştır. Total intravenöz anestezi (TIVA) tekniğiyle birinci gruptaki hastalara propofol infüzyonu, ikinci gruptakilere ise tiyopental uygulandı. Hastalardan operasyondan 30 dk önce, 30 dk ve 24 saat sonra alınan kanlarda immunolojik ve hematolojik tetkikler yapıldı. Ayrıca hastalara anestezi indüksiyonundan 2 gün önce ve sonra tüberkülin testi uygulandı. Çalışmamız sonucunda, 1. grupta postoperatif 30. dk'da IgG, IgM, IgA ve C3, ikinci grupta ise IgM, IgA ve C4 düzeylerindeki azalma anlamlı bulundu ($p<0.05$). Postoperatif 24. saatte 1. grupta IgG, IgM ve C3'teki artma ile IgA'daki azalma, 2. grupta ise IgA'daki azalma anlamlı idi ($p<0.05$). Gruplar arası fark karşılaştırıldığında postoperatif 30. dk ile 24. saat arasında IgA'daki azalmanın farkları anlamlı bulundu ($p<0.05$). Her iki grupta da CD4, lökosit ve lenfositdeki azalma anlamlı idi ($p<0.05$). Postoperatif 24. saatte CD4, CD8 ve lenfosit değerleri 1. grupta anlamlı artarken 2. grupta sadece lenfosit artımı anlamlı bulundu ($p<0.05$). Gruplar arası fark araştırıldığında 1. gruptaki lökosit ve lenfosit değerlerindeki azalma anlamlı idi ($p<0.05$). Tüberkülin testi postop. 2. gün ölçüm sonuçlarının her iki grupta da anlamlı derecede azaldığı görüldü ($p<0.05$). Propofolün daha belirgin olmak üzere her iki ajanın da immunsüpresif etkisi olduğu tespit edildi. [Turgut Özal Tıp Merkezi Dergisi 1997;4(2):187-192]

Anahtar Kalimeler: *Propofol, tiyopental, immun sistem*

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Much of the immunological changes seen after a surgical operation is due to direct effect of some anaesthetic agents used or their contribution to operational trauma or endocrine response. Effect of the anaesthesia may differ due to breaking point of stress response, individual immune status, period and/or method of anaesthesia and chemical structure of anaesthetic agent while effect of operation on immune status is due to extension of the operation and individual stress response (1).

The immune system recognises foreign molecules and readily reacts against them. There is no definite tissue or organ in which the immune system is located. Components of the system are found nearly all parts of the body. They are normally stable whereas they migrate towards stimulus when a foreign molecule, a mutagenic or pathologic activity is detected (2).

Total intravenous anaesthesia (TIVA), which means transient loss of some reflexes and sense by loss of consciousness without interfering with vital functions at bulbus, become more common TIVA,of which hypnotic effect is provided by intravenous anaesthetic infusion, is an easy, rapid, secure and also economic way of anaesthesia (3-5).

Altough it's new, propofol containing purified egg phosphatide, NaOH, soya bean oil and water is widely accepted as an anaesthetic agent (4,6-8). Propofol is a short-term anaesthetic of which effect starts just after 30 seconds from application and patient is early and quickly arousable after anaesthesia. Additionaly, it has very few post-op side-effects like nausea, vomiting and headache (9,10).

On the other hand thiopentone sodium (sodium ethyl-1 methyl buttyl thiobarbutirate) is the most commonly used and to be experienced with, and is among the barbutirates with very short-term effectivity (11,12).

MATERIAL AND METHODS

With approval from our instituonal ethic committee, this study was carried out on specimens were drawn 40 adult patients. Venous blood 30 minutes before and after the operation and 24 hours later. The blood specimens obtained were from those are taking no premedication, having no tumoral pathology or immune deficiency and being operated at Selçuk University Medical Faculty General Surgery division. The immunologic study was carried out at microbiology department.

The patients were separeted into 2 groups. By means of infusion pump, propofol at a dose of 2-2.5 mg/kg infusion and 6-12 mg/kg/h maintance was given to the first group by the TIVA while thiopentone at a dose of 3-5mg/kg infusion and 7mg/kg/h maintance was given to the second group. Anesthetic gas wasn't used. As being muscle relaxant Atracurium Besilate and Fentanyl for analgesia were applied on all patients.

The PPD test was performed on all patients before and after the 48 hours from operation and endurations were graded as 3 groups. Normal venous blood for haemotologic tests (CBC, Blood Smear, Total Lymphocyte Count) and immunologic tests (IgG, IgM, IgA, C3-C4) and heparinised blood for lymphocyte subgroups (CD3-CD4) were drawn.

Immunoglobulins and complements were measured by Radial Immunodiffusion (Kallested Lab. Chaska, USA) method while lymphocyte subgroups were evaluated by means of anti-clonal antibodies (Sero-tek anti-human antibodies, England) and of Olympus PM 10 AD immunoflorascent microscope (13,14).

All data was analysed by paired and intergroup unpaired tests. Significence level was accepted as $p<0,05$.

RESULTS

The 2 groups were similiar for ages, weights and anaesthesia-periods ($p>0,05$) (Table 1). Post-op 30^{th} minute IgM, IgA, IgG and C3 concentrations were significiantly different than of preoperative concentrations in the group propofol applied by TIVA but C4 concentrations of pre-op and post-op periods were not significantly different (Table 2).

In the thiopentone applied group decreasing in IgM, IgA, C4 concentrations were significant while decreasing in IgG and C3 concentrations were insignificant (Table 3). When a comparision was

made between the concentrations at post-op 30th minute and 24 th hour in the first group, increase in serum IgM, IgG and C3 and decrease in serum IgA were statistically significant (p<0,05) while there were no significiance for changes of IgG and C4 concentrations (p>0,05) (Table 2). On the other hand, the concentrations in the thiopentone applied group there was no significant increasing in IgG,IgM,IgA,C3,C4 (p>0,05) (Table3).

When immunoglobulin and compleman concentrations of the both groups were matched, there was a significant decrease in IgG concentrations at both pre-op and post-op 30 th minutes and in IgA concentrations at post-op 30th minute and 24th hour in the propofol applied group (p<0,05).

When CD4, CD8, leucocyte and lymphocyte values were compared between the both groups, there was a significant decreasing in leucocyte and lymphocyte numbers of that group in which propofol applied (p>0,05) while a significant, change was not found in CD4 and CD8 values of the both groups (p>0,05) (Table 4).

Decreasing in CD4, leucocyte and lymphocyte values of the propofol applied group was significant whereas of the other group was unsignificant (p<0,05) (Table 5) Values at post-op 30 th minute and 24 th hour in the both groups were also unsignificant (p>0,05) (Table 5).

The PPD test was applied on all patients. A significiance was found between pre-op (2 days before) and post-op (2 days later) enduration diameters (p<0,05) where as there was no significiance between the both groups (p>0,05).

DISCUSSION

Altough anaesthetic agents have usually an inhibitory effect on bacterial growth (5), they may depress directly or/and indirectly the immune system by means of hormones thus may increase infection risk, may depress healing or may facilitate spreading of malign disorders(5,15).

One must analyse the immunoglobulins and complement system,which are variables of the immune system, in order to determine effects of anaesthetic agents on humoral immune system.

Propofol's effect on humoral immune system was compared with of isoflorin in a study (16), and reported that IgA and IgM consantransions had decreased, IgG consantransions had increased in

Table 1. Demographic characteristics of the patiens

	1. group (Propofol)	2. group (Thiopentone)*
n	20	20
Sex (F/M)	10/10	14/6
Age (Year)	38.4±11.4	39.5±8.82
Weigth (Kg)	72.9±12.9	71.5±14.7
Tıme of anesthesia (min)	84.5±22.65	76.0±21.74

* p>0.05 (There is no statistical difference between two groups).

Table 2. Mean serum IgG, M, A, and C3-C4 concentrations at pre-op 30th, post-op 30th minutes and post-op 24th hour in the case of using propofol

	Pre-op	Post-op 30th min.	Post-op 24th hr
IgG	1625.0±356.7*	1247.5±414.7	1355.0±527.0
IgM	160.75±19.62*	138.25±39.5***	176.5±61.3
IgA	187.9±93.1*,**	136.8±49.5***	116.5±45.1
C_3	153.85±33.18*	139.15±28.5***	149.5±29.46
C_4	39.3±9.15	37.55±13.68	41.35±15.74

* p<0.05 at pre-op and post-op 30 th minutes.
** p<0.05 at pre-op and post-op 24 th hours.
*** p<0.05 at post-op 30 th minutes and post-op 24 th hours.

Table 3. Mean serum IgG, M, A and C3-C4 values at pre-op 30th, post-op 30th minutes and post-op 24 th hour in the case of using the propofol

	Pre-op	Post-op 30th min.	Post-op 24th hr
IgG	1108.0±461	1050.0±406.2	1062.0±592
IgM	212.0±119.5*	186.5±87.3	196.5±110.2
IgA	235.7±109*,**	143.8±49.1	152.5±72.2
C_3	120.9±31.53	113.75±24.43	120.75±29.35
C_4	29.9±9.56*	26.2±10.04	27.25±12.77

* p<0.05 at pre-op and post-op 30th Min.
** p<0.05 at preop and post-op 24th hours.

Table 4. Mean CD3-CD4 leucocyte and lymphocyte numbers at pre-op 30th, post-op 30 th minutes and post-op 24 th hour in the case of using propofol

	Pre-op	Post-op 30th min.	Post-op 24th hr
CD_4	40.8±6.07**	43.15±11.6***	50.25±8.99
CD_8	53.55±7.29*	45.95±5.31***	49.25±1.92
Leucocyte	11435±3136*,**	9653±3263	9500±3089
Lymphocyte	61.5±5.3*,**	54.65±6.67***	58.95±4.05

* p<0.05 at pre-op and post-op 30th Min.
** p<0.05 at pre-op and post-op 24th hours.
*** p<0.05 at post-op 30th Min. and post-op 24th hours.

Table 5. Mean CD3-CD4 leucocyte and lymphocyte numbers at pre-op 30th, post-op 30th minutes and post-op 24 th hour in the case of using thiopentone

	Pre-op	Post-op 30th min.	Post-op 24th hr
CD_4	39.35±4.0	36.8±7.9	40.15±5.98
CD_8	44.5±8.89*	41.2±7.42	44.8±6.17
Leucocyte	7365±3271*,**	6760±2589	6720±2592
Lymphocyte	58.4±5.09*	56.1±5.52***	58.05±4.24

* $p<0.05$ at pre-op and post-op 30th Min.
** $p<0.05$ at pre-op and post-op 24th hours.
*** $p<0.05$ at post-op 30th Min. and post-op 24th hours.

isofloran applied cases at 4th day whereas IgM and a consantransions had decreased and there had been no change in IgA consantransions. In another study by Erol et al (17) to reveal for revealing effects of propofol anaesthesia on the humoral immune systems, they applied the anaestehetic agent at a dose of 2 mg/kg for induction and 7 mg/kg for maintance on 23 adults and measured immunoglobulin and complement consantransions before and after anaesthesia and 4 days later by the turbidometry method. They found significant decreasing in IgG, IgM, IgA and C4 in the post-op period and in IgG and IgM consantransions at the post-op 4th day, and also significant increase in C3, C4 at the post-op 4th day.

Doenicke et al. (18) applied 2 mg/kg propofol for induction on 32 volunter healthy adults, made waken them without exposing any operation then measured their serum immmunoglobulin and complement consantransions by laser nepholmetry and racet immunoelectrophoresis respectavely. before anaesthesia and 1 day later, and did not found a significant change. These contradicting results of the 2 researches may be due to differences in methods, and, as in Doenickes, having no surgical operation and applying low-dose propofol. We found that there was a significent decrease in IgG, M and A consantransions at post-op 30th minute, and in IgA consantransions at post-op 24th hour in the propofol applied group by TIVA. Decreasing of IgA at post-op 30 minute may be due to hemodilution but decreasing of IgA, at post-op 24th hour is due to anaestehetic agent. Other immunoglobulin consantransions begun increasing towards 24th hour due to disappering of the dilutional effect. This also may be due to patients to began oral taking, neurohumoral changes developed by stress reaction to turn back normal and hemodilutional effect to go away gradually. Lasting of decreasing IgA consantransions until the 24th hour is contrary to the other studies. We found IgM and IgA to be decreased and IgG to be unchanged in the Thiopentone applied group. Unchanging consantransions of IgG, a pillar of humoral immune system, indicates unimportence of the immunosuppression caused by anaesthetic agents.

Decrease in IgA, and IgM were in harmony with some studies in which halathone, enflorone spiral anaesthesia, neurolept anaesthesia, acupuncture or fentanyl by transcutan stimulation had been applied, but unchanging of IgG was contrary to their results (16,19-21). Thiopentone had a smaller effect than propofol on the comlement system while decreasing in C4 level at post-op 30th minute was an unexpected one in our study.

A decrease in IgA leads local infections whereas a decreased IgM delays primary immune response. Most important duty in immune response is of IgG. For that reason its supposed that thiopentone does not effect the immunity very much altough it may increase risk for infection. Tough propofol may increase risk for infection and interfere with body defence system, it does not effect local immunity leading ineffective immune response. Main function of the complement system is related to the humoral immunity. The system also play an important role in host defence by regulating the leucocyte migration and easing the lysosomes to come out from the phagocytes. Therefore decrease in their serum consantransions may not be throughly correlated with those of immunoglobulins. However serum compleman consantransions increase in the event of an increase in any case of increasing humoral immunresponse.

Erol et al. (17) reported that C4 consantransions had decreased after operation whereas C3 and C4 consantransions had significiantly increased at post-op 4th day. In another study (16) it was found that decrease in C3 and C4 consantransions in isofluran applied cases and decrease just in C4 in propofol applied cases at post-op 30th minute were considerable whereas increasing of C3 and C4 consantransions in both propofol and isofluran applied cases at post-op 4th day were significant. Doenicke et al. observed no significiant variation in complemant consantransions in their study (18).

At post-op 30th minute, decreasing of C4 consantransions in the thiopentone applied group and of C3 consantransions in the propofol applied group were observed in our study, It's also observed that there was a significant increasing of C3 in the propofol applied cases at 24th hour. İncreasing of C3, which has anaphylo toxic and chemotoxic activities suggests humoral and cellular immunoresponse activation.

It's reported that, after researching by the PHA method, both propofol and thiopentone had positive effect on activation of the T cells, B cells, CD4 and CD8. Propofol had more effect on the CD4 activation (15) NK activity in that study reported to be decreased. Decrease in CD4 activity is in hormony with that one reported by Pirttikangas et al where as increase in CD8 activity is contrary to that (22).

Observation of no significant change except decreasing of CD4 in the thiopentone applied group is similar to the findings by Salo et al. (20). To reveal thiopenton's effect on the immunosystem in general and on the spinal anaesthesia, changes in the T, Th, Ts, NK cells, IgG, IgM and IgA concentrations were measured and no significant variation was observed (20).

Relative decrease in leucocyte and lymphocyte counts and unsignificiance of the difference between both groups may be depend on hemodilution. Enduration diameters of the PPD significantly decreased after anaesthesia and operation. This was more prominent in the propofol applied group and in harmony with the other variations in cellular and humoral immunity parameters.

In conclusion we compared effects of propofol and thiopentan on the immune system at humoral and cellular points and found propofol to have greater effect. This may depend on directly chemical structure of the propofol (soya bean oil, egg-phospolipid and gliserol) or indirectly cytokines mediated by the agents. Altought the propofol has a less toxic effect relative to other anaestehetics in immunodepressive patients.

It's immunosuppressive in vitro because of its lipid gradient at higher concentrations (23,24). On the other hand when compared with the thiopentone the propofol has a more increasing effect on TNF - alpha and IL-1 alpha sysnthesis, and a more decreasing effect on IL-1ß and th-2 sysnthesis while has no effect on IL-6, TNF syntehsis (18,25,26). We suggest that on must be carefull while choosing patients for the propofol anesthesia because of its considerable immunosupressive effect. So it's wisefull not to use propofol as anesthetic in cases in which immunosupression may be risky, i.e. those taking immunosupressive drugs and -if it's used- patients must be properly protected aganist the infection risk in the short term post-op period.

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